

411

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: U.S. Patent No. 4,344,949 :  
Patentee: Milton L. Hoefle and : Box:  
Sylvester Klutchko : Patent  
Issue Date: August 17, 1982 : Extension

REQUEST FOR EXTENSION OF PATENT TERM

UNDER 35 U.S.C. 156

Honorable Commissioner of Patents  
and Trademarks  
Washington, D.C. 20231

NOV 27 1982

Sir:

Pursuant to Section 201(a) of the Drug Price Competition and Patent Term Restoration Act of 1984, 35 U.S.C. Sec. 156, WARNER-LAMBERT COMPANY, of 201 Tabor Road, Morris Plains, New Jersey, 07950, assignee of the above-identified patent by an assignment from the inventors to WARNER-LAMBERT COMPANY, recorded February 20, 1981, at Reel 3871, Frames 826-827, hereby requests an extension of the patent term of United States Patent No. 4,344,949.

The following information is submitted in accordance with 35 U.S.C. Sec. 156(d) and 37 C.F.R. 1.740, and follows the numerical format set forth in 37 C.F.R. 1.740.

(1) A complete identification of the approved product by appropriate chemical and generic name, physical structure characteristics:

The approved product is ACCUPRIL® (quinapril hydrochloride) tablet. The active ingredient in ACCUPRIL® tablet is quinapril hydrochloride. ACCUPRIL® tablet is for oral administration.

Chemically it is 2-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-3-isoquinoline carboxylic acid, hydrochloride (S,S,S), or 2-[2-[[1-ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydroisoquinoline carboxylic acid monohydrochloride, [3S-[2[R\*(R\*)],3R\*]] (see USAN 1991).

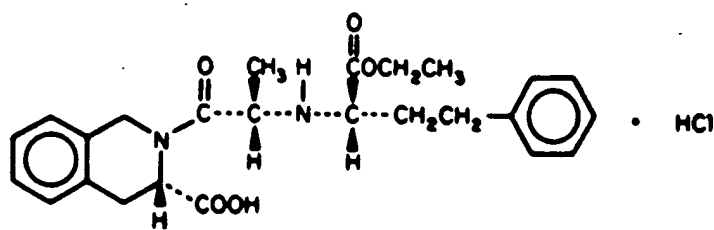
The stereochemical descriptor, [3S-[2[R\*(R\*)],3R\*]], for the attached structure describes the single isomer of this substance for which the three chiral centers all have an "S" configuration as defined in the Cahn-Ingold-Prelog stereochemical nomenclature system. The descriptor is written following conventions used by Chemical Abstracts Service, Columbus, Ohio.

In describing the configuration of atoms in a molecule, this system uses the designation "R" or "S" to define one chiral center (known as the reference center) absolutely and then describes all other chiral centers in relation to the reference center, using relative descriptors such as cis, trans,  $\alpha$ ,  $\beta$ , R\*, or S\*. R\* and S\* are relative descriptors that describe centers of the same configuration as (R\*), or opposite configuration from (S\*), the reference center.

In the case of quinapril hydrochloride where centers exist both in the ring and in the side chain attached to the ring, the center in the ring is the reference center to which the others are related. The "3S" describes the 3 position on the isoquinoline ring as having an absolute configuration of S. The [2[R\*(R\*)] describes the two centers in the side chain at the 2 position as absolute configuration. The 3R\* is purely conventional and refers to the 3 position in the ring because the system requires the reference center to have a relative descriptor in addition to the absolute descriptor.

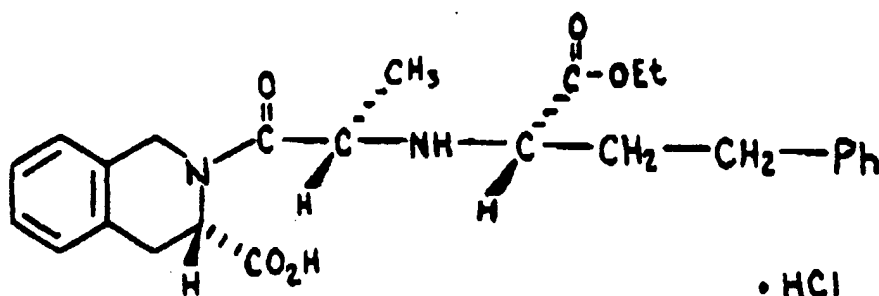
The name CI-906 hydrochloride (CI-906) is the internal name used by WARNER-LAMBERT COMPANY.

Quinapril hydrochloride has the structural formula shown by each of the following:



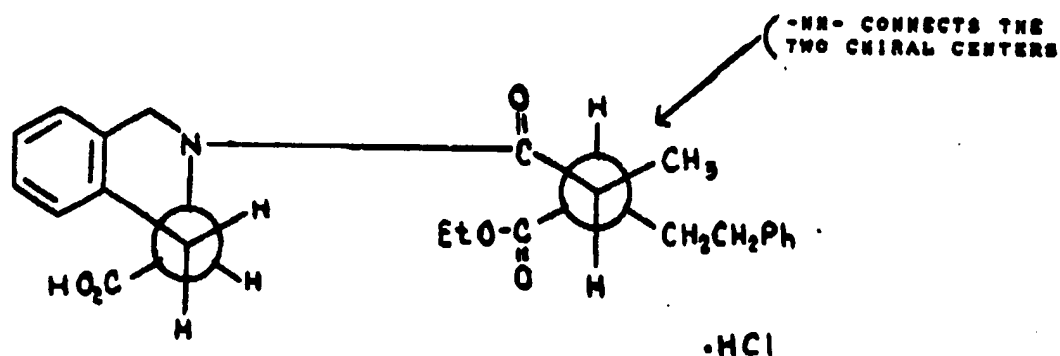
USAN

or



FLYING-WEDGE PROJECTION

or



NEWMAN PROJECTION

As noted above, ACCUPRIL® tablet is a pharmaceutical composition containing quinapril hydrochloride for oral use; see the section entitled DESCRIPTION, DOSAGE AND ADMINISTRATION in Exhibit 1 (PACKAGE INSERT) which is the Product Information sheet for the approved product.

(2) A complete identification of the Federal statute including the applicable provision of law under which the regulatory review occurred:

The regulatory review occurred under Section 505 of the Federal Food, Drug and Cosmetic Act ("FFDCA"), 21 U.S.C. Sec. 301 et seq. Section 505 provides for the submission and approval of new drug applications ("NDAs") for antihypertension products.

(3) An identification of the date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred:

ACCUPRIL® (quinapril hydrochloride) tablet was approved by the Food and Drug Administration ("FDA") for commercial marketing pursuant to Section 505(b) of the FFDCA on November 19, 1991; see Exhibit 2 (APPROVAL LETTER).

(4) In the case of a human drug product, an identification of each active ingredient in the product and as to each active ingredient, a statement that it has not been previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act, or a statement of when the active ingredient was approved for commercial marketing or use (either alone or in combination with other active ingredients) and the provision of law under which it was approved.

The only active ingredient in ACCUPRIL® (quinapril hydrochloride) tablet is quinapril hydrochloride. Quinapril hydrochloride has not been previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act.



(5) A statement that the application is being submitted within the sixty day period permitted for submission pursuant to Sec. 1.720(f) and an identification of the last day on which the application could be submitted.

The product was approved for commercial marketing on November 19, 1991, and the last day within the sixty day period permitted for submission of an application for extension of the patent is January 18, 1991. The date of submission of the present application is no later than January 18, 1991, and therefore, the present application has been timely filed.

(6) A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue, and the date of expiration:

U.S. PATENT NO. 4,344,949

INVENTORS: Milton Louis Hoefle  
and Sylvester Klutchko

Issue Date: August 17, 1982

Expiration Date: August 17, 1999

(7) A copy of the patent for which an extension is being sought including the entire specification (including claims) and drawings:

A copy of U.S. Patent 4,344,949 is attached as Exhibit 3 (PATENT).

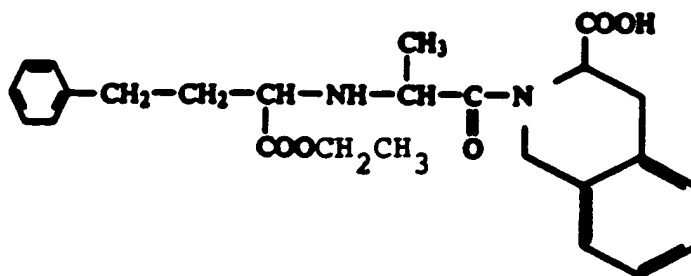
(8) A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or re-examination certificate issued in the patent:

No disclaimer, certificate of correction or re-examination certificate has been issued. No maintenance fee is required.

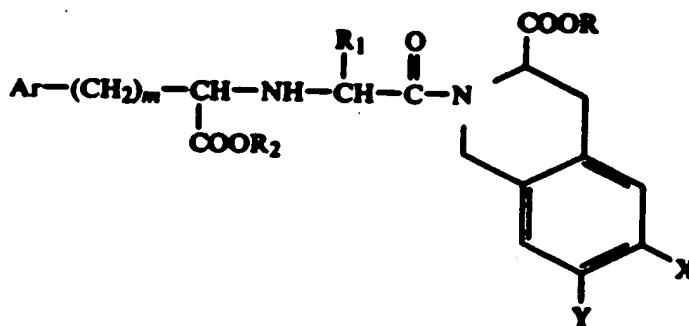
(9) A statement that the patent claims the approved product or a method of using or manufacturing the approved product, and a showing which lists each applicable patent claim and demonstrates the manner in which each applicable patent claim reads on the approved product or a method of using or manufacturing the approved product:

The patent claims quinapril hydrochloride, the active ingredient of the approved product, ACCUPRIL® tablet, generically in claims 1, 2, and 4.

The structural formula for quinapril hydrochloride is the S,S,S, configuration of the following formula:



Structural formula of the compounds claimed in Claim 1 is as follows:

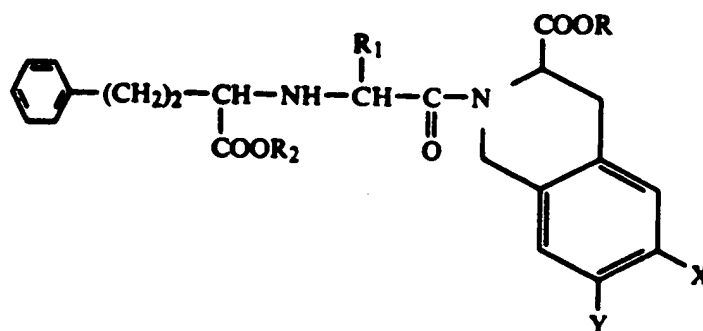


It is evident from a comparison of the two structural formulas that R, X and Y in the formula of Claim 1 of the patent must each be hydrogen, and R<sub>1</sub> must be methyl, R<sub>2</sub> must be ethyl, m must be 2 and Ar must be phenyl for the compound defined by structural formula to read on quinapril.

Claim 1 contains the required definitions of these substituents to read on quinapril.

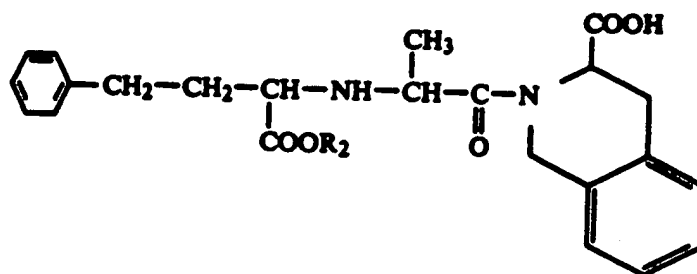
Claims 2 and 4 are also generic to quinapril.

Claim 2 contains the following structural formula:



Thus the Claim 2 formula differs from the formula of Claim 1 in that the Ar substituent is shown as phenyl, m is shown as 2, and R, R<sub>1</sub>, R<sub>2</sub>, X and Y are more narrowly defined but still read on quinapril.

Claim 4 contains the following structural formula:



The Claim 4 formula differs from the formula of Claim 1 in that in addition to the Ar shown as phenyl, the  $(CH_2)_m$  is shown as  $CH_2CH_2$ ,  $R_1$  is shown as  $CH_3$ , R is shown as hydrogen, X and Y are each shown as hydrogen and  $R_2$  is more narrowly defined but still reads on quinapril.

Claim 13 claims 2-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]-amino]-1-oxopropyl]-1,2,3,4-tetrahydro-3-isoquinoline carboxylic acid, hydrochloride (S,S,S) which is quinapril hydrochloride.

In addition, each of Claims 1, 2, 4, and 13 read on a pharmaceutically acceptable salt of quinapril which includes hydrochloride.

Claim 14 claims a pharmaceutical composition comprising 10 to 500 mg of a compound defined according to Claim 1 or a pharmaceutically acceptable salt thereof. Therefore, Claim 14 reads on all DOSAGES of the approved product, ACCUPRIL® tablet (quinapril hydrochloride).

Claim 15 is for a method of treating hypertension by administering an effective amount of a compound defined in Claim 1 or a pharmaceutically acceptable salt thereof which reads on quinapril hydrochloride. Claim 15 reads on the ADMINISTRATION of the approved product, ACCUPRIL® tablet (quinapril hydrochloride).

(10) A statement beginning on a new page, of the relevant dates and information pursuant to 35 U.S.C. Sec. 156(g) in order to enable the Secretary of Health and Human Services to determine the applicable regulatory review period as follows:

(i) For a patent claiming a human drug, antibiotic or human biological product, the effective date of the investigational new drug (IND) application and the IND number; the date on which a new drug application (NDA) was initially submitted and the NDA number; and the date on which the NDA was approved:

On May 17, 1982, Parke-Davis Pharmaceutical Research Division of WARNER-LAMBERT COMPANY, the patent owner, submitted to the Food and Drug Administration ("FDA") a "Notice of Claimed Investigational Exemption for a New Drug" (hereinafter referred to as an "IND") for CI-960 hydrochloride (quinapril hydrochloride) tablet. A copy of this letter is submitted herewith as Exhibit 4 (IND SUBMISSION LETTER)

The IND was assigned number 20,336. The IND became effective on June 18, 1982, which is thirty days after receipt of the IND by the FDA; see Exhibit 5 (IND ACKNOWLEDGMENT LETTER) attached hereto. This establishes the beginning of the "regulatory review period" under 35 U.S.C. 156(g)(1) as June 18, 1982.

On January 26, 1989, a new drug application (NDA 19,885) was initially submitted under Section 505(b) of the Federal Food, Drug, and Cosmetic Act (FFDCA) for ACCUPRIL® (quinapril hydrochloride) tablet. A copy of the cover letter of January 26, 1989, is submitted herewith as Exhibit 6 (NDA SUBMISSION LETTER).

This NDA was approved on November 19, 1991. Attached as Exhibit 2 (APPROVAL LETTER) is a copy of a letter dated November 19, 1991, from the FDA to WARNER-LAMBERT approving the NDA for the preparation ACCUPRIL® (quinapril hydrochloride) tablet.

Thus, for the purposes of determining the "regulatory review period" under 35 U.S.C. 156(g)(1), November 19, 1991, is the date of the first approval of quinapril hydrochloride, which is the active ingredient in ACCUPRIL® tablet.

(11) A brief description, beginning on a new page, of the significant activities undertaken by the applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities:

As described above in item (10), WARNER-LAMBERT COMPANY submitted an IND for quinapril hydrochloride tablet on May 17, 1982, which became effective on June 18, 1982, and, in close consultation with FDA, subsequently conducted clinical studies under this IND. The studies under the IND are summarized in the attached Exhibit 7 (IND LOG) entitled "REGULATORY LIAISON AND COMPLIANCE MANAGEMENT SYSTEM CI NUMBER 906 APPLICATION NUMBER=20,336." These studies were used to support the new drug application submitted by WARNER-LAMBERT COMPANY on January 26, 1989.

Subsequent to the submission of this NDA, WARNER-LAMBERT COMPANY had numerous contacts and meetings with the FDA with respect to the application and these are summarized in the attached Exhibit 8, (NDA LOG) entitled "REGULATORY LIAISON AND COMPLIANCE INFORMATION MANAGEMENT SYSTEM CI NUMBER= 906 APPL. NUMBER= 19-885."

(12) A statement, beginning on a new page, that in the opinion of the applicant the patent is eligible for the extension and a statement as to the length of the extension claimed, including how the length of extension was determined:

Statement of Eligibility of the Patent for Extension  
Under 35 U.S.C. Sec. 156(a) and (c)(4)

Section 156(a) provides, in relevant part, that the term of a patent which claims a product, a method of using a product, or a method of manufacturing a product shall be extended if (1) the term of the patent has not expired before an application for extension is submitted, (2) the term of the patent has never been extended, (3) the application for extension is submitted by the owner of record of the patent or its agent in accordance with 35 U.S.C. Sec. 156(d), (4) the product has been subject to a regulatory review period before its commercial marketing or use, and (5) the permission for the commercial marketing or use of the product after such regulatory review period is the first permitted commercial marketing or use of the product under the provision of law under which such regulatory review period occurred; and Section 156(c)(4) provides, that in no event shall more than one patent be extended for the same regulatory review period for any product.

As described by corresponding number, each of these elements is satisfied here:

- (1) The term of U.S. Patent No. 4,344,949 expires on August 17, 1999. This application has, therefore, been submitted before the expiration of the patent term. In addition, there is no required



maintenance fee because the patent was filed before a maintenance fee was effected and the patent is in force.

- (2) The term of this patent has never been extended.
- (3) This application is submitted by the owner of record, WARNER-LAMBERT COMPANY, (Assignment recorded on February 20, 1981, at Reel 3871, Frames 826-827). This application is submitted in accordance with 35 U.S.C. Sec. 156(d) in that it is submitted within the sixty-day period beginning on the date, November 19, 1991, that the product received permission for marketing under the Federal Food Food, Drug and Cosmetic Act and contains the information required under 35 U.S.C. Sec. 156(d).
- (4) As evidenced by the November 19, 1991, letter from the FDA, Exhibit 2, (APPROVAL LETTER) the product was subject to a regulatory review period under Section 505(b)(1) of the FFDCA before its commercial marketing or use.
- (5) The permission for the commercial marketing of ACCUPRIL® (quinapril hydrochloride) tablet after regulatory review under Section 505(b)(1) is the first permitted commercial marketing of quinapril hydrochloride. This is confirmed by the absence of any approved new drug application under which quinapril hydrochloride could be commercially marketed prior to November 19, 1991.

- (6) No other patent has been extended for the same regulatory period for the approved product (Section 156(c)(4)).

Statement as to Length of Extension Claimed

In Accordance With 37 C.F.R. 1.775

The term of U.S. Patent No. 4,344,949 should be extended for a period of 2 years to August 17, 2001.

The period of extension is determined in accordance with 35 U.S.C. Section 156 and follows the format set forth in 37 CFR 1.775(c) and (d).

37 CFR 1.775(c) The length of the regulatory review period for a human drug, antibiotic drug or human biological product will be determined by the Secretary of Health and Human Services. Under 35 U.S.C. 156(g)(1)(B), it is the sum of --

(1) The number of days in the period beginning on the date an exemption under subsection (i) of section 505 or subsection (d) of section 507 of the Federal Food, Drug, and Cosmetic Act became effective for the approved product and ending on the date the application was initially submitted for such product under those sections or under section 351 of the public Health Service Act;

The number of days between the effective date of the initial IND, June 18, 1982, and the initial submission of the NDA, January 26, 1989, is a period of 2414 days

and

(2) The number of days in the period beginning on the date the application was initially submitted for the approved product under section 351 of the Public Health Service Act, subsection (b) of section 505 or section 507 of the Federal Food, Drug, and Cosmetic Act and ending on the date such application was approved under such section.

The number of days between the initial submission of the NDA, January 26, 1989, to NDA approval, November 19, 1991, is a period of 1027 days.

37 C.F.R. 1.775(d) The term of the patent as extended for a human drug, antibiotic drug or human biological product will be determined by--

(1) Subtracting from the number of days determined by the Secretary of Health and Human Services to be in the regulatory review period:

(i) The number of days in the periods of paragraphs (c)(1) and (c)(2) of this section which were on and before the date on which the patent issued;

The number of days in the period of the IND, effective on June 18, 1982, which were on or before August 17, 1982, the date the patent was issued, is a period of 60 days,

2414 days minus 60 days equals 2354 days,

and

the number of days in the period of the NDA, effective on January 26, 1989, which

were on or before August 17, 1982, the date the patent was issued, is a period of 0 days,

1027 days minus 0 days equals 1027 days.

(ii) The number of days in the periods of paragraphs (c)(1) and (c)(2) of this section during which it is determined under 35 U.S.C. 156(d)(2)(B) by the Secretary of Health and Human Services that applicant did not act with due diligence;

The number of days the applicant did not act with due diligence is 0 days,

therefore,

2354 days minus 0 days equals 2354 days.

1027 days minus 0 days equals 1027 days.

(iii) One-half the number of days remaining in the period defined by paragraph (c)(1) of this section after that period is reduced in accordance with paragraphs (d)(1)(i) and (ii) of this section; half days will be ignored for purposes of subtraction;

One-half of 2354 days equals 1177 days.

Thus U.S. Patent No. 4,344,949 should be entitled to an extension of 2204 days (1177 days plus 1027 days).

(2) By adding the number of days determined in paragraph (d)(1) of this section to the original term of the patent as shortened by any terminal disclaimer;

Adding 2204 days to August 17, 1999,  
the original term of the patent (no terminal disclaimer was made),  
extends the term to August 29, 2005.

(3) By adding 14 years to the date of approval of the application under section 351 of the Public Health Service Act, or subsection (b) of section 505 or section 507 of the Federal Food, Drug, and Cosmetic Act;

Adding 14 years to November 19, 1991,  
the date of approval of the application,  
gives the date of November 19, 2005.

(4) By comparing the dates for the ends of the periods obtained pursuant to paragraphs (d)(2) and (d)(3) of this section with each other and selecting the earlier date;

The earlier date is August 29, 2005.

(5) If the original patent was issued after September 24, 1984,

This is not applicable for the patent.

(6) If the original patent was issued before September 24, 1984, and

(i) If no request was submitted for an exemption under subsection (i) of section 505 or subsection (d) of section 507 of the Federal Food, Drug, and Cosmetic Act before September 24, 1984, by--

This is not applicable for the patent.

(ii) If a request was submitted for an exemption under subsection (i) of section 505 or subsection (d) of section 507 of the Federal Food, Drug, or Cosmetic Act before September 24, 1984 and the commercial marketing or use of the product was not approved before September 24, 1984, by--

(A) Adding 2 years to the original expiration date of the patent or earlier date set by terminal disclaimer,

Adding 2 years to August 17, 1999 equals  
August 17, 2001.

(B) By comparing the dates obtained pursuant to paragraphs (d)(4) and (d)(6)(ii)(A) of this section with each other and selecting the earlier date.

August 17, 2001 is the earlier date.

(13) Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and to the Secretary of Health and Human Services any information which is material to any determination to be made relative to the application for extension.

WARNER-LAMBERT COMPANY filed an NDA application with respect to the combination of quinapril hydrochloride plus hydrochlorothiazide tablets. The IND with respect to the tablets was assigned number 34-487 and the NDA was assigned number 20-125 which has not yet been approved. ACCUPRIL® tablet is the first quinapril hydrochloride containing product approved by the FDA.

**(14) Prescribed Fee:**

The prescribed fee of \$600.00 for receiving and acting on this application for extension of patent term is hereby authorized. Please charge Deposit Account No. 23-0450 in the amount of the fee above, or such greater or lesser amount of excess fees as the Commissioner determines is required by law.

**(15) The name, address and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed:**

Joan Thierstein  
Registration No. 29,450  
Patent Department  
WARNER-LAMBERT COMPANY  
2800 Plymouth Road  
Ann Arbor, Michigan 48105  
Telephone: (313) 996-7190

**(16) A duplicate of the application papers, certified as such.**

A duplicate of the application papers, certified as such, is submitted herewith.

**(17) An oath or Declaration as set forth in paragraph (b) of 37 C.F.R. 1.740.**

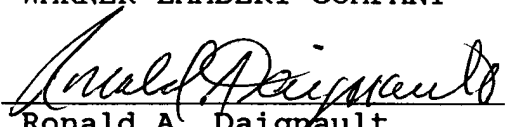
DECLARATION

The undersigned is authorized to obligate WARNER-LAMBERT COMPANY, the owner of record of U.S. Patent 4,344,949, which has applied for an extension of term of this patent, I declare that, I have reviewed and understand the contents of this application being submitted pursuant to this section; that I believe that the patent is subject to extension pursuant to 37 C.F.R. 1.710; that I believe that the length of extension claimed is fully justified under 35 U.S.C. 156 and the applicable regulations; and that I believe that the patent for which this extension is being sought meets the conditions for extension of the term of a patent as set forth in 37 C.F.R. 1.720.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application and any extension of U.S. Patent No. 4,344,949.

WARNER-LAMBERT COMPANY

By:

  
Ronald A. Daigault

Reg. No. 25,968

Assistant Secretary

WARNER-LAMBERT COMPANY

Pharmaceutical Research Division

2800 Plymouth Road

Ann Arbor, Michigan 48105

(313) 996-7530

Date:

November 25, 1991

JT1S3943.DOC



# 19

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**CERTIFICATE OF MAILING (37 CFR 1.10)**

"Express Mail" No: \_\_\_\_\_ Date of Deposit \_\_\_\_\_

I hereby certify that this transmittal together with the application for extension of patent term under 35 U.S.C. 156 referred to below is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Commissioner of Patents and Trademarks, Washington D.C. 20231.

\_\_\_\_\_  
Name of Person Mailing Paper

\_\_\_\_\_  
Signature

\*\*\*\*\*

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re : U.S. Patent No. 4,344,949  
Issued : August 17, 1982  
Patentee(s) : Milton L. Hoefle and  
Sylvester Klutchko  
For : SUBSTITUTED ACYL DERIVATIVES OF 1,2,3,4-  
TETRAHYDROISOQUINOLINE-3-CARBOXYLIC ACIDS

Attention: Charles Van Horn  
BOX: PATENT TERM EXTENSION  
Commissioner of Patents and Trademarks  
Washington, D.C. 20231

**TRANSMITTAL OF AN APPLICATION**  
**FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. 156**

Sir:

Transmitted herewith is an APPLICATION FOR EXTENSION OF PATENT TERM (an original and a certified duplicate original with declaration and attachments thereto) of the above-captioned patent for a product approved on November 19, 1991.

- [ ] The application is being mailed by Express Mail under 37 CFR 1.10 and the required Certificate of Mailing appears above. The use of this certificate is intended to insure that the application will be considered as timely filed.
- [X] A prescribed fee in the amount of \$600.00 is required for the application presented.

Please charge Deposit Account No. 23-0450 in the amount of the fee above, or such greater or lesser amount of fees for the application as the Commissioner determines is required by law. This letter is submitted in triplicate.

- [X] Three working copies of the APPLICATION FOR EXTENSION OF PATENT TERM and attachments to each are provided for the convenience of the U.S. Patent and Trademark Office.

Respectfully submitted,

November 25, 1991  
Date



JOAN THIERSTEIN, Attorney  
Registration No. 29,450  
Warner-Lambert Company  
2800 Plymouth Road  
Ann Arbor, MI 48105  
Tel. (313)996-7190

- Attachments:
- [X] An original APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. 156 with Declaration and attachments thereto
  - [X] A certified duplicate original APPLICATION FOR EXTENSION OF PATENT TERM with Declaration and attachments thereto
  - [X] Three working copies of APPLICATION FOR EXTENSION OF PATENT TERM with Declaration and attachments thereto
  - [X] Form WL-1 (transmittal - in triplicate)

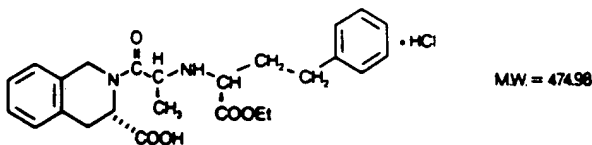
**PACKAGE INSERT**

# Accupril® (Quinapril Hydrochloride Tablets)

## DESCRIPTION

ACCUPRIL® (quinapril hydrochloride) is the hydrochloride salt of quinapril, the ethyl ester of a non-sulfhydryl angiotensin-converting enzyme (ACE) inhibitor, quinapril.

Quinapril hydrochloride is chemically described as [3S-[(2R(R\*),3R\*)]-2-[2-[(1-ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-1,5-benzodiazepine-5-carboxylic acid, monohydrochloride. Its empirical formula is  $C_{24}H_{30}N_2O_5 \cdot HCl$  and its structural formula is



Quinapril hydrochloride is a white to off-white amorphous powder that is freely soluble in aqueous solvents.

ACCUPRIL tablets contain 5 mg, 10 mg, 20 mg, or 40 mg of quinapril for oral administration. Each tablet also contains candellila wax, croscopolones, gelatin, lactose, magnesium carbonate, magnesium stearate, synthetic red iron oxide, and titanium dioxide.

## CLINICAL PHARMACOLOGY

**Mechanism of Action:** Quinapril is deesterified to the principal metabolite, quinaprilat, which is an inhibitor of ACE activity in human subjects and animals. ACE is a peptidyl dipeptidase that catalyzes the conversion of angiotensin I to the vasoconstrictor, angiotensin II. The effect of quinapril in hypertension appears to result primarily from the inhibition of circulating and tissue ACE activity thereby reducing angiotensin II formation. Quinapril has the effect in blood pressure caused by intravenously administered angiotensin I, but has no effect on the pressor response to angiotensin II, norepinephrine or epinephrine. Angiotensin II also stimulates the secretion of aldosterone from the adrenal cortex, thereby facilitating renal sodium and fluid reabsorption. Reduced aldosterone secretion by quinapril may result in a small increase in serum potassium. In controlled hypertension trials, treatment with ACCUPRIL alone resulted in mean increases in potassium of 0.07 mmol/L (see PRECAUTIONS). Removal of angiotensin II negative feedback on renin secretion leads to increased plasma renin activity (PRA).

While the principal mechanism of antihypertensive effect is thought to be through the renin-angiotensin-aldosterone system, quinapril exerts antihypertensive actions even in patients with low renin hypertension. ACCUPRIL was an effective antihypertensive in all races studied, although it was somewhat less effective in blacks (usually a predominantly low renin group) than in nonblacks. ACE is identical to kininase II, an enzyme that degrades bradykinin, a potent peptide vasodilator; whether increased levels of bradykinin play a role in the therapeutic effect of quinapril remains to be elucidated.

**Pharmacokinetics and Metabolism:** Following oral administration, peak plasma quinapril concentrations are observed within one hour. Based on recovery of quinapril and its metabolites in urine, the extent of absorption is at least 80%. The rate and extent of quinapril absorption are diminished moderately (approximately 25-30%) when ACCUPRIL tablets are administered during a high-fat meal. Following absorption, quinapril is deesterified to its major active metabolite, quinaprilat (about 38% of oral dose), and to other minor inactive metabolites. Following multiple oral dosing of ACCUPRIL, there is an effective accumulation half-life of quinaprilat of approximately 3 hours, and peak plasma quinaprilat concentrations are observed approximately 2 hours post-dose. Quinaprilat is eliminated primarily by renal excretion, up to 96% of an IV dose, and has an elimination half-life in plasma of approximately 2 hours and a prolonged terminal phase with a half-life of 25 hours. The pharmacokinetics of quinapril and quinaprilat are linear over a single-dose range of 5-80 mg doses and 40-160 mg in multiple daily doses. Approximately 97% of either quinapril or quinaprilat circulating in plasma is bound to proteins.

In patients with renal insufficiency, the elimination half-life of quinaprilat increases as creatinine clearance decreases. There is a linear correlation between plasma quinaprilat clearance and creatinine clearance. In patients with end-stage renal disease, chronic hemodialysis or continuous ambulatory peritoneal dialysis has little effect on the elimination of quinapril and quinaprilat. Elimination of quinaprilat is reduced in elderly patients ( $\geq 65$  years); this reduction is attributable to decrease in renal function (see DOSAGE AND ADMINISTRATION), and not to age itself. Quinaprilat concentrations are reduced in patients with alcoholic cirrhosis due to impaired deesterification of quinapril. Studies in rats indicate that quinapril and its metabolites do not cross the blood-brain barrier.

**Pharmacodynamics and Clinical Effects:** Single doses of 20 mg of ACCUPRIL provide over 80% inhibition of plasma ACE for 24 hours. Inhibition of the pressor response to angiotensin I is short-acting, with a 20 mg dose giving 75% inhibition for about 4 hours, 50% inhibition for about 8 hours, and 20% inhibition at 24 hours. With chronic dosing, however, there is substantial inhibition of angiotensin II levels at 24 hours by doses of 20-80 mg.

Administration of 10 to 80 mg of ACCUPRIL to patients with mild to severe hypertension results in a reduction of sitting and standing blood pressure to about the same extent with minimal effect on heart rate. Symptomatic postural hypotension is infrequent although it can occur in patients who are salt- and/or volume-depleted (see WARNINGS). Antihypertensive activity commences within 1 hour with peak effects usually achieved by 2 to 4 hours after dosing. During chronic therapy, most of the blood pressure lowering effect of a given dose is obtained in 1-2 weeks. In multiple-dose studies, 10-80 mg per day in single or divided doses lowered systolic and diastolic blood pressure throughout the dosing interval, with a trough effect of about 5-11/3-7 mm Hg. The trough effect represents about 50% of the peak effect. While the dose-response relationship is relatively flat, doses of 40-80 mg were somewhat more effective at trough than 10-20 mg, and twice daily dosing tended to give a somewhat lower trough blood pressure than once daily dosing with the same total dose. The antihypertensive effect of ACCUPRIL continues during long-term therapy, with no evidence of loss of effectiveness.

Hemodynamic assessments in patients with hypertension indicate that blood pressure reduction produced by quinapril is accompanied by a reduction in total peripheral resistance and renal vascular resistance with little or no change in heart rate, cardiac index, renal blood flow, glomerular filtration rate, or filtration fraction.

Use of ACCUPRIL with a thiazide diuretic gives a blood-pressure lowering effect greater than that seen with either agent alone.

In patients with hypertension, ACCUPRIL 10-40 mg was similar in effectiveness to captopril, enalapril, propranolol, and thiazide diuretics.

Therapeutic effects appear to be the same for elderly ( $\geq 65$  years of age) and younger adult patients given the same daily dosages, with no increase in adverse events in elderly patients.

## INDICATIONS AND USAGE

ACCUPRIL is indicated for the treatment of hypertension. It may be used alone or in combination with thiazide diuretics.

In using ACCUPRIL, consideration should be given to the fact that another angiotensin converting enzyme inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen vascular disease. Available data are insufficient to show that ACCUPRIL does not have a similar risk (see WARNINGS).

## CONTRAINDICATIONS

ACCUPRIL is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor.

## Accupril® (Quinapril Hydrochloride Tablets)

## WARNINGS

**Angioedema:** Angioedema of the face, extremities, lips, tongue, glottis, and larynx has been reported in patients treated with ACE inhibitors and has been seen in 0.1% of patients receiving ACCUPRIL. Angioedema associated with laryngeal edema can be fatal. If laryngeal stridor or angioedema of the face, tongue, or glottis occurs with treatment with ACCUPRIL, should be discontinued immediately. The patient treated in accordance with accepted medical care, and carefully observed until the swelling disappears. In instances where swelling is confined to the face and lips, the condition generally resolves without treatment. Antihistamines may be useful in relieving symptoms. Where there is involvement of the tongue, glottis, or larynx likely to cause airway obstruction, emergency therapy including, but not limited to, subcutaneous epinephrine solution 1:1000 (0.3 to 0.5 mL), should be promptly administered (see ADVERSE REACTIONS).

**Hypotension:** Symptomatic hypotension was rarely seen in uncomplicated hypertensive patients treated with ACCUPRIL, but, as with other ACE inhibitors, it is a possible consequence of therapy in salt/volume depleted patients, such as those previously treated with diuretics or dietary salt restriction or who are on dialysis (see PRECAUTIONS, DRUG INTERACTIONS, AND ADVERSE REACTIONS). In controlled studies, syncope was observed in 0.4% of patients (N=3203); this incidence was similar to that observed for captopril (1%) and enalapril (0.8%).

In patients with concomitant congestive heart failure, with or without associated renal insufficiency, ACE inhibitor therapy may cause excessive hypotension, which may be associated with oliguria or azotemia and, rarely, with acute renal failure and death. In such patients, ACCUPRIL therapy should be started at the recommended dose under close medical supervision. These patients should be followed closely for the first 2 weeks of treatment and whenever the dosage of antihypertensive medication is increased (see DOSAGE AND ADMINISTRATION).

If symptomatic hypotension occurs, the patient should be placed in the supine position and, if necessary, normal saline may be administered intravenously. A transient hypotensive response is not a contraindication to further doses; however, lower doses of ACCUPRIL or reduced concomitant diuretic therapy should be considered.

**Neutropenia/Agranulocytosis:** Another ACE inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression rarely in patients with uncomplicated hypertension, but more frequently in patients with renal impairment, especially if they also have a collagen vascular disease, such as systemic lupus erythematosus or scleroderma. Agranulocytosis did occur during ACCUPRIL treatment in one patient with a history of neutropenia during previous captopril therapy. Available data from clinical trials of ACCUPRIL are insufficient to show that, in patients without prior reactions to other ACE inhibitors, ACCUPRIL does not cause agranulocytosis at similar rates. As with other ACE inhibitors, periodic monitoring of white blood cell counts in patients with collagen vascular disease and/or renal disease should be considered.

**Fetal/Maternal Morbidity and Mortality:** ACE inhibitors, including ACCUPRIL, can cause fetal and neonatal morbidity and mortality when administered to pregnant women.

When ACE inhibitors have been used during the second and third trimesters of pregnancy, there have been reports of hypotension, renal failure, skull hypoplasia, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function. Oligohydramnios has been associated with fetal limb contractures, craniofacial deformities, hypoplastic lung development and intra-uterine growth retardation. Prematurity and patent ductus arteriosus have been reported, although it is not clear whether these occurrences were due to the ACE-inhibitor exposure or to the mother's underlying disease. It is not known whether exposure limited to the first trimester can adversely affect fetal outcome.

A patient who becomes pregnant while taking ACE inhibitors, or who takes ACE inhibitors when already pregnant, should be apprised of the potential hazard to her fetus. If she continues to receive ACE inhibitors during the second or third trimester of pregnancy, frequent ultrasound examinations should be performed to look for oligohydramnios. When oligohydramnios is found, ACE inhibitors should generally be discontinued.

Infants with histories of in utero exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Hemodialysis and peritoneal dialysis have little effect on the elimination of quinapril and quinaprilat.

No fetotoxic or teratogenic effects were observed in rats at quinapril doses as high as 300 mg/kg/day (180 and 300 times the maximum daily human dose when based on mg/kg and mg/m<sup>2</sup>, respectively), despite maternal toxicity at 150 mg/kg/day, tested later in gestation and during lactation. Reduced offspring body weight was seen at 2.25 mg/kg/day and changes in renal histology (justaglomerular cell hypertrophy, tubulointerstitial dilation, glomerulosclerosis) were observed both in dams and offspring treated with 150 mg/kg/day. Quinapril was not teratogenic in the rabbit; however, as noted with other ACE inhibitors, maternal toxicity and embryotoxicity were seen in some rabbits at quinapril doses as low as 0.5 mg/kg/day (one time the recommended human dose) and 1.0 mg/kg/day, respectively.

## PRECAUTIONS

### General

**Impaired renal function:** As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors, including ACCUPRIL, may be associated with oliguria and/or progressive azotemia and rarely acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine have been observed in some patients following ACE inhibitor therapy. These increases were almost always reversible upon discontinuation of the ACE inhibitor and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy.

Some hypertensive patients with no apparent preexisting renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when ACCUPRIL has been given concomitantly with a diuretic. This is more likely to occur in patients with preexisting renal impairment. Dosage reduction and/or discontinuation of any diuretic and/or ACCUPRIL may be required.

Evaluation of hypertensive patients should always include assessment of renal function (see DOSAGE AND ADMINISTRATION).

**Hyperkalemia and potassium-sparing diuretics:** In clinical trials, hyperkalemia (serum potassium  $\geq 5.5$  mmol/L) occurred in approximately 2% of patients receiving ACCUPRIL. In most cases, elevated serum potassium levels were isolated values which resolved despite continued therapy. Less than 0.1% of patients discontinued therapy due to hyperkalemia. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with ACCUPRIL (see PRECAUTIONS, Drug Interactions).

**Surgery/Anesthesia:** In patients undergoing major surgery or during anesthesia with agents that produce hypotension, ACCUPRIL will block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

### Information for Patients

**Angioedema:** Angioedema, including laryngeal edema can occur with treatment with ACE inhibitors, especially following the first dose. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to stop taking the drug until they have consulted with their physician (see WARNINGS).

**Symptomatic hypotension:** Patients should be cautioned that lightheadedness can occur, especially during the first few days of ACCUPRIL therapy, and that it should be reported to a physician if actual syncope occurs. Patients should be told to not take the drug until they have consulted with their physician (see WARNINGS).

All patients should be cautioned that inadequate fluid intake or excessive perspiration, diarrhea, or vomiting can lead to an excessive fall in blood pressure because of reduction in fluid volume with the same consequences of lightheadedness and possible syncope.

Patients planning to undergo surgery and/or anesthesia should be told to inform their physician that they are taking an ACE inhibitor.

**Hyperkalemia:** Patients should be told not to use potassium supplements or salt substitutes containing potassium without consulting their physician (see PRECAUTIONS).

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0527FA001

## Accupril® (Quinapril Hydrochloride Tablets)

**Neutropenia:** Patients should be told to report promptly any indication of infection (eg, sore throat, fever) which could be a sign of neutropenia.

**NOTE:** As with many other drugs, certain advice to patients being treated with ACCUPRIL is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

### Drug Interactions

**Concomitant diuretic therapy:** As with other ACE inhibitors, patients on diuretics, especially those on recently instituted diuretic therapy, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with ACCUPRIL. The possibility of hypotensive effects with ACCUPRIL may be minimized by either discontinuing the diuretic or cautiously increasing salt intake prior to initiation of treatment with ACCUPRIL. If it is not possible to discontinue the diuretic, the starting dose of quinapril should be reduced (see DOSAGE AND ADMINISTRATION).

**Agents increasing serum potassium:** Quinapril can attenuate potassium loss caused by thiazide diuretics and increase serum potassium when used alone. If concomitant therapy of ACCUPRIL with potassium-sparing diuretics (eg, spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes is indicated, they should be used with caution along with appropriate monitoring of serum potassium (see PRECAUTIONS).

**Tetracycline and other drugs that interact with magnesium:** Simultaneous administration of tetracycline with ACCUPRIL reduced the absorption of tetracycline by approximately 26% to 37%, possibly due to the high magnesium content in ACCUPRIL tablets. This interaction should be considered if coprescribing ACCUPRIL and tetracycline or other drugs that interact with magnesium.

**Lithium:** Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving concomitant lithium and ACE inhibitor therapy. These drugs should be coadministered with caution and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, it may increase the risk of lithium toxicity.

**Other agents:** Drug interaction studies of ACCUPRIL with other agents showed:

- Multiple dose therapy with propranolol or cimetidine has no effect on the pharmacokinetics of single doses of ACCUPRIL.
- The anticoagulant effect of a single dose of warfarin (measured by prothrombin time) was not significantly changed by quinapril coadministration twice daily.
- ACCUPRIL treatment did not affect the pharmacokinetics of digoxin.
- No pharmacokinetic interaction was observed when single doses of ACCUPRIL and hydrochlorothiazide were administered concomitantly.

### Carcinogenesis, Mutagenesis, Impairment of Fertility

Quinapril hydrochloride was not carcinogenic in mice or rats when given in doses up to 75 or 100 mg/kg/day (50 to 60 times the maximum human daily dose, respectively, on an mg/m<sup>2</sup> basis and 3.8 to 10 times the maximum human daily dose when based on an mg/m<sup>2</sup> basis) for 104 weeks. Female rats given the highest dose level had an increased incidence of mammary lymph node hyperplasia and squamous metaplasia of the uterine endometrium. Neither quinapril nor quinaprilate were mutagenic in the Ames bacterial assay with or without metabolic activation. Quinapril was also negative in the following genetic toxicology studies: *in vitro* mammalian cell point mutation, sister chromatid exchange in cultured mammalian cells, micronucleus test with mice, *in vitro* chromosome aberration with V79 cultured lung cells, and *in vivo* cytogenetic study with rat bone marrow. There were no adverse effects on fertility or reproduction in rats at doses up to 100 mg/kg/day (60 and 10 times the maximum daily human dose when based on mg/m<sup>2</sup> and mg/m<sup>2</sup>, respectively).

### Pregnancy

**Pregnancy Category D:** See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

### Nursing Mothers

It is not known if quinapril or its metabolites are secreted in human milk. Quinapril is secreted to a limited extent, however, in milk of lactating rats (5% or less of the plasma drug concentration was found in rat milk). Because many drugs are secreted in human milk, caution should be exercised when ACCUPRIL is given to a nursing mother.

### Genetic Use

Elderly patients exhibited increased area under the plasma concentration time curve (AUC) and peak levels for quinapril compared to values observed in younger patients; this appeared to relate to decreased renal function rather than to age itself. In controlled and uncontrolled studies of ACCUPRIL, where 918 (21%) patients were 65 years and older, no overall differences in effectiveness or safety were observed between older and younger patients. However, greater sensitivity of some older individual patients cannot be ruled out.

### Pediatric Use

The safety and effectiveness of ACCUPRIL in children have not been established.

### ADVERSE REACTIONS

ACCUPRIL has been evaluated for safety in 1960 subjects and patients. Of these, 3203 patients, including 655 elderly patients, participated in controlled clinical trials. ACCUPRIL has been evaluated for long-term safety in over 1400 patients treated for 1 year or more.

Adverse experiences were usually mild and transient.

Discontinuation of therapy because of adverse events was required in 4.7% of patients treated with ACCUPRIL in placebo-controlled hypertension trials.

Adverse experiences probably or possibly related to therapy or of unknown relationship to therapy occurring in 1% or more of the 1563 patients in placebo-controlled hypertension trials who were treated with ACCUPRIL are shown below.

Adverse Events in Placebo-Controlled Trials

	Accupril (N=1563) Incidence (Discontinuation)	Placebo (N=579) Incidence (Discontinuation)
Headache	5.8 (0.7)	10.9 (0.7)
Dizziness	3.9 (0.6)	2.6 (0.2)
Fatigue	2.6 (0.3)	1.0
Coughing	2.0 (0.5)	0.0
Nausea and/or Vomiting	1.4 (0.3)	1.9 (0.2)
Abdominal Pain	1.0 (0.2)	0.7

Clinical adverse experiences probably or possibly related, or of uncertain relationship to therapy occurring in 0.5% to 1.0% (except as noted) of the patients treated with ACCUPRIL (with or without concomitant diuretic) in controlled or uncontrolled trials (N=4397) and less frequent, clinically significant events seen in clinical trials or post-marketing experience (the rarer events are in italics) include listed by body system:

**General:** back pain, malaise

**Cardiovascular:** palpitation, vasodilation, tachycardia, heart failure, hyperkalemia, myocardial infarction, cerebrovascular accident, hypertensive crisis, angina pectoris, orthostatic hypotension, cardiac rhythm disturbances

**Gastrointestinal:** dry mouth or throat, constipation, gastrointestinal hemorrhage, pancreatitis, abnormal liver function tests

**Nervous/Psychiatric:** somnolence, vertigo, syncope, nervousness, depression

**Integumentary:** increased sweating, pruritus, exfoliative dermatitis, photosensitivity reaction

**Urogenital:** acute renal failure

**Other:** amyotrophy, pharyngitis, sinusitis, bronchitis, agranulocytosis, thrombocytopenia

### Angioedema

Angioedema has been reported in patients receiving ACCUPRIL (0.1%). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis, and/or larynx occurs, treatment with ACCUPRIL should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

### Clinical Laboratory Test Findings

**Hematology:** (See WARNINGS)

**Hypertension:** (See PRECAUTIONS)

## Accupril® (Quinapril Hydrochloride Tablets)

**Creatinine and Blood Urea Nitrogen:** Increases ( $>1.25$  times the upper limit of normal) in serum creatinine and blood urea nitrogen were observed in 2% and 2%, respectively, of patients treated with ACCUPRIL alone; increases are more likely to occur in patients receiving concomitant diuretic therapy than in those on ACCUPRIL alone. These increases often remit on continued therapy.

### OVERDOSAGE

No data are available with respect to overdosage in humans. Doses of 1440 to 4260 mg/kg of quinapril cause significant emesis in mice and rats.

The most likely clinical manifestation would be symptoms attributable to severe hypotension.

Laboratory determinations of serum levels of quinapril and its metabolites are not widely available, and such determinations have, in any event, no established role in the management of quinapril overdose.

No data are available to suggest physiological maneuvers (eg, maneuvers to change pH of the urine) that might accelerate elimination of quinapril and its metabolites.

Hemodialysis and peritoneal dialysis have little effect on the elimination of quinapril and quinaprilate. Angiotensin II could presumably serve as a specific antagonist-antidote in the setting of quinapril overdose, but angiotensin II is essentially unavailable outside of scattered research facilities. Because the hypotensive effect of quinapril is achieved through vasodilation and effective hypovolemia, it is reasonable to treat quinapril overdose by infusion of normal saline solution.

### DOSAGE AND ADMINISTRATION

**Monotherapy:** The recommended initial dosage of ACCUPRIL in patients not on diuretics is 10 mg once daily. Dosage should be adjusted according to blood pressure response measured at peak (2-6 hours after dosing) and trough (predosing). Generally, dosage adjustments should be made at intervals of at least 2 weeks. Most patients have required dosages of 20, 40, or 80 mg/day, given as a single dose or in 2 equally divided doses. In some patients treated once daily, the antihypertensive effect may diminish toward the end of the dosing interval. In such patients an increase in dosage or twice daily administration may be warranted. In general, doses of 40-80 mg and divided doses give a somewhat greater effect at the end of the dosing interval.

**Concomitant Diuretics:** If blood pressure is not adequately controlled with ACCUPRIL monotherapy, a diuretic may be added. In patients who are currently being treated with a diuretic, symptomatic hypotension occasionally can occur following the initial dose of ACCUPRIL. To reduce the likelihood of hypotension, the diuretic should, if possible, be discontinued 2 to 3 days prior to beginning therapy with ACCUPRIL (see WARNINGS). Then, if blood pressure is not controlled with ACCUPRIL alone, diuretic therapy should be resumed.

If the diuretic cannot be discontinued, an initial dose of 5 mg ACCUPRIL should be used with careful medical supervision for several hours and until blood pressure has stabilized.

The dosage should subsequently be titrated (as described above) to the optimal response (see WARNINGS, PRECAUTIONS, and Drug Interactions).

**Renal Impairment:** Kinetic data indicate that the apparent elimination half-life of quinapril increases as creatinine clearance decreases. Recommended starting doses, based on clinical and pharmacokinetic data from patients with renal impairment, are as follows:

Creatinine Clearance	Maximum Recommended Initial Dose
$>60$ mL/min	10 mg
30-60 mL/min	5 mg
10-30 mL/min	2.5 mg
$<10$ mL/min	Insufficient data for dosage recommendation

Patients should subsequently have their dosage titrated (as described above) to the optimal response. Elderly ( $\geq 65$  years): The recommended initial dosage of ACCUPRIL in elderly patients is 10 mg given once daily followed by titration (as described above) to the optimal response.

### HOW SUPPLIED

ACCUPRIL tablets are supplied as follows:

5-mg tablets: brown, film-coated, elliptical, scored tablets, coded "PD 527" on one side and "5" on the other.

N0071-0527-23 bottles of 90 tablets

10-mg tablets: brown, film-coated, triangular, scored tablets, coded "PD 530" on one side and "10" on the other.

N0071-0530-23 bottles of 90 tablets

N0071-0530-40 10 x 10 unit dose blisters

20-mg tablets: brown, film-coated, round, scored tablets, coded "PD 532" on one side and "20" on the other.

N0071-0532-23 bottles of 90 tablets

N0071-0532-40 10 x 10 unit dose blisters

40-mg tablets: brown, film-coated, elliptical, scored tablets, coded "PD 535" on one side and "40" on the other.

N0071-0535-23 bottles of 90 tablets

N0071-0535-40 10 x 10 unit dose blisters

Dispense in well-closed containers as defined in the USP.

Storage: Store at controlled room temperature 15°-30°C (59°-86°F).

Caution—Federal law prohibits dispensing without prescription.

Issued August 1991

**PARKE-DAVIS**  
Div of Warner-Lambert Co  
Morris Plains, NJ 07950 USA

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Accupril  
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**APPROVAL LETTER**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

NDA 19-885

Food and Drug Administration  
Rockville MD 20857

NOV 19 1991

Parke-Davis Pharmaceutical Research Division  
Warner-Lambert Company  
Attention: Irwin G. Martin, Ph.D.  
2808 Plymouth Road  
Ann Arbor, MI 48106-1047

Dear Dr. Martin:

Please refer to your January 26, 1989 new drug application submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Accupril (quinapril hydrochloride) 5, 10, 20, and 40 mg Tablets.

We also acknowledge receipt of your amendments and correspondence dated May 23 and 24, August 20, 21, 22, 26 (two), 29 and 30, September 4, 9, and 13, October 2 and 18 (two) and November 4, 1991.

We have completed the review of this application and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the final printed labeling submitted September 9, 1991 (package insert) and August 26, September 9 and 16, and October 18, 1991 (carton and container labels). Accordingly, the application is approved effective on the date of this letter.

In addition, we are reviewing the proposed advertising campaign that was submitted on August 26 and October 2, 1991. We note that in your August 30, 1991 conversation with Ms. Kathleen Bongiovanni, you agreed to meet with the Division of Drug Marketing, Advertising, and Communications to discuss your campaign prior to the marketing of Accupril Tablets.

Please submit one market package of the drug when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Ms. Kathleen Bongiovanni  
Consumer Safety Officer  
(301) 443-4730

Sincerely yours,

Robert Temple, M.D.  
Director  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

**PATENT**



[54] **SUBSTITUTED ACYL DERIVATIVES OF  
1,2,3,4-TETRAHYDROISOQUINOLINE-3-  
CARBOXYLIC ACIDS**

[75] Inventors: Milton L. Hoefle; Sylvester Klutchko,  
both of Ann Arbor, Mich.

[73] Assignee: Warner-Lambert Company, Morris  
Plains, N.J.

[21] Appl. No.: 236,397

[22] Filed: Feb. 20, 1981

**Related U.S. Application Data**

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abandoned.

[51] Int. Cl.<sup>3</sup> ..... A61K 31/47; C07D 217/16;  
C07D 491/048

[52] U.S. Cl. .... 424/258; 546/90;  
546/141; 546/142; 546/147

[58] Field of Search ..... 546/141, 90, 142, 147;  
424/258

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*Primary Examiner*—Donald G. Daus

*Assistant Examiner*—James H. Turnipseed

*Attorney, Agent, or Firm*—Walter Patton

[57] **ABSTRACT**

Substituted acyl derivatives of 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acids and the pharmaceutically acceptable salts thereof are produced by coupling a suitably substituted 1,2,3,4-tetrahydroisoquinoline with a suitably substituted amino acid and when desired hydrolyzing or removing protecting groups of the resulting product. The compounds of the invention, their salts and pharmaceutical compositions thereof are useful as antihypertensive agents.

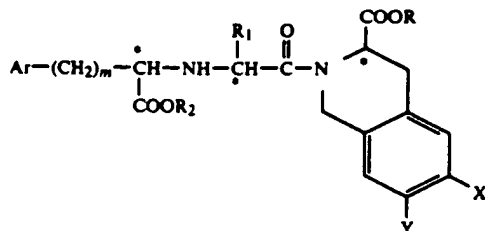
**15 Claims, No Drawings**

# SUBSTITUTED ACYL DERIVATIVES OF 1,2,3,4-TETRAHYDROISOQUINOLINE-3-CAR- BOXYLIC ACIDS

This is a continuation-in-part of copending United States Patent application U.S. Ser. No. 193,767, filed Oct. 3, 1980, now abandoned.

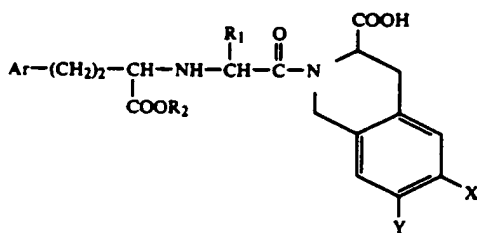
## SUMMARY AND DETAILED DESCRIPTION

The invention relates to substituted acyl derivatives of 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid compounds having the formula



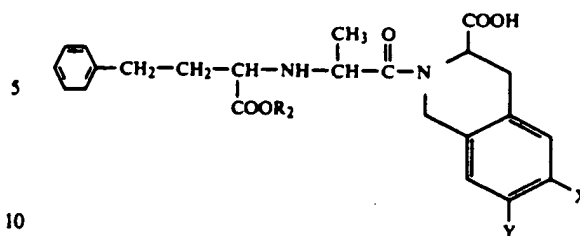
where R is hydrogen, lower alkyl or aralkyl; R<sub>1</sub> is hydrogen, lower alkyl, or benzyl; R<sub>2</sub> is hydrogen or lower alkyl, and Ar is phenyl or phenyl substituted with 1 or 2 substituents selected from the group consisting of fluorine, chlorine, bromine, lower alkyl, lower alkoxy, hydroxy or amino; X and Y are independently hydrogen, lower alkyl, lower alkoxy, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, hydroxy, or X and Y together are methylenedioxy; m is 0 to 3; and the pharmaceutically acceptable acid salts thereof.

Preferred compounds of the invention are acylated 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acids having the formula



where R<sub>1</sub> is hydrogen or lower alkyl containing 1 to 3 carbon atoms, R<sub>2</sub> is hydrogen or lower alkyl containing 1 to 3 carbon atoms and Ar is phenyl, and phenyl substituted in the para position by fluorine, chlorine, bromine, methyl, hydroxy, methoxy or amino, X and Y are as defined above; and pharmaceutically acceptable acid salts thereof.

Further preferred compounds of the invention are acylated 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acids having the formula



where R<sub>2</sub> is hydrogen or lower alkyl containing 1 to 3 carbon atoms X and Y are independently hydrogen or lower alkoxy and pharmaceutically acceptable acid salts thereof; and specifically the compounds designated 2-[2-[(1-carboxy-3-phenylpropyl)amino]-1-oxopropyl]-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid; 2-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid; 2-[2-[(1-carboxy-3-phenylpropyl)amino]-1-oxopropyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylic acid; 2-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylic acid; and pharmaceutically acceptable acid salts thereof.

The terms "lower alkyl" and "lower alkoxy" are intended to mean a straight or branched alkyl group of from one to four carbon atoms.

The compounds of the invention of formula I have asymmetric carbon atoms indicated by asterisks. The 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid used in this invention has the L (S) configuration. This configuration has been shown to be required for biological activity, and thus active compounds of the invention are derived from either L(-) or DL-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acids.

Optical and diastereo isomers arising from the chirality at the centers marked with an asterisk in formula I and racemates and mixtures thereof are within the scope of this invention. The S configuration at these centers is preferred.

The compounds of the invention may exist in anhydrous form as well as in solvated, including hydrated forms. In general, the hydrated forms and the solvated forms with pharmaceutically acceptable solvents are equivalent to the anhydrous or unsolvated form for the purposes of the invention.

The compounds of the invention of formula I may be prepared from 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid by first protecting the carboxylic acid group, preferably as an ester, e.g., with a lower alkyl, benzyl or trimethylsilyl group. The protected carboxylic acid compound is coupled to an N-protected amino acid, e.g., glycine or L-alanine, protected on nitrogen with t-butyloxycarbonyl or benzyloxycarbonyl. The coupling is carried out by any of a variety of standard peptide coupling techniques as disclosed, for example, in "The Peptides. Analysis, Synthesis, Biology, Vol. 1 Major Methods of Peptide Bond Formation, Part A", ed. E. Gross, J. Meierhofer, Academic Press N.Y. (1979). An especially useful method involves the use of a dehydrating agent, such as dicyclohexylcarbodiimide alone or in the presence of reagents forming reactive esters, e.g., 1-hydroxybenzotriazole, in suitable aprotic solvents such as dimethylformamide, acetonitrile, tetrahydrofuran or chlorinated hydrocarbons. This gives the intermediate (N-protected-2-aminoacyl)-1,2,3,4-tet-

rahydroisoquinoline-3-carboxylic acid esters. These may then be either partially or totally deblocked depending on the protecting groups chosen, using anhydrous acids, e.g., hydrochloric acid in acetic acid or trifluoroacetic acid in methylene chloride, or hydrogen gas and a catalyst to give the intermediate dipeptide either in free form or protected as an ester.

The compounds of the invention of formula I may then be prepared by reacting the intermediate dipeptide or its ester derivative with  $\alpha$ -keto-4-substituted phenylbutyric acid or its lower alkyl ester derivatives under dehydrating and reducing conditions. Preferred dehydrating agents include molecular sieves in aprotic solvents and preferred reducing agents include sodium cyanoborohydride or hydrogen gas with a catalyst.

Alternatively, the dipeptide or its ester derivative may be reacted with an  $\alpha$ -halo-4-substituted phenylbutyric acid or its ester in the presence of a suitable basic reagent, such as triethylamine or alkali carbonates or bicarbonates, in a solvent, to give the compounds of the invention of formula I. Ester protected products may be hydrolyzed under basic or acidic reaction conditions to free acid derivatives, or, in the case of benzyl esters, catalytic hydrogenolysis may be preferred.

Alternately, compounds of the invention of formula I may be prepared in a different manner. This consists of applying either of the two methods described above for the attachment of the 2-(4-phenylbutyric acid) moiety to the protected dipeptide, first to glycine or L-alanine, which may be protected as an ester, to give N-[2-(4-phenylbutyric acid)]-substituted glycine or L-alanine derivative.

After selective deblocking of the acid moiety on the glycine or alanine portion of the product, the resulting monoacid may be coupled, either directly or subsequent to suitable blocking of the amino group, via standard peptide coupling procedures to the 1,2,3,4-tetrahydro-3-isoquinoline carboxylate, protected as an ester. Selective or complete removal of the ester groups and any amine protecting groups yield the compounds of formula I.

The products are obtained typically as a mixture of diastereoisomers which can be separated by standard methods of fractional crystallization or chromatography.

The compounds of this invention form acid salts with various inorganic and organic acids which are also within the scope of the invention. The pharmaceutically acceptable acid addition salts of the compounds of the present invention may be prepared by conventional reactions by reacting the free amino acid or amino ester form of the product with one or more equivalents of the appropriate acid providing the desired anion in a solvent or medium in which the salt is insoluble, or in water and removing the water by freeze drying. The salts of strong acids are preferred. As exemplary, but not limiting, of pharmaceutically acceptable acid salts are the salts of hydrochloric, hydrobromic, sulfuric, nitric, acetic, fumaric, malic, maleic and citric acids.

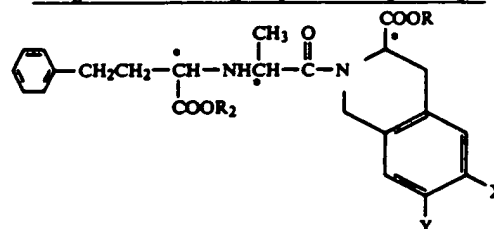
The action of the enzyme renin on angiotensinogen, a pseudoglobulin in blood plasma, produces the decapeptide angiotensin I. Angiotensin I is converted by angiotensin converting enzyme (ACE) to the octapeptide angiotensin II. The latter is an active pressor substance which has been implicated as the causative agent in various forms of hypertension in various mammalian species, e.g., rats and dogs. The compounds of this invention intervene in the renin->angiotensin I->angio-

tensin II sequence by inhibiting angiotensin I converting enzyme and reducing or eliminating the formation of the pressor substance angiotensin II, and therefore are useful in reducing or relieving hypertension. Thus by the administration of a composition containing one or a combination of compounds of formula I or pharmaceutically acceptable salts thereof, hypertension in the species of mammal suffering therefrom is alleviated. A single dose, or preferably two to four divided daily doses, provided on a basis of about 0.1 to 100 mg per kilogram per day, preferably about 1 to 50 mg per kilogram per day, is appropriate to reduce blood pressure. The substance is preferably administered orally, but parenteral routes such as subcutaneously, intramuscularly, intravenously or intraperitoneally can also be employed.

In vitro ACE Assay: Angiotensin converting enzyme (ACE) inhibitory activity was determined by assaying guinea pig serum ACE in the presence and absence of the test compound. ACE from guinea pig serum and the test compounds were preincubated for 10 minutes before the addition of the labelled substrate  $^3\text{H}$ -hippuryl-glycyl-glycine. After a 60 minute incubation of  $37^\circ\text{C}$ . the reaction was stopped by the addition of 0.1 N HCl. ACE cleaves the hippuryl-glycyl bond to form the dipeptide glycyl-glycine and  $^3\text{H}$ -hippuric acid. The  $^3\text{H}$ -hippuric acid was then extracted with ethyl acetate and the ACE activity of a given sample calculated as the amount of  $^3\text{H}$ -hippuric acid generated.

TABLE

Acyl Derivatives of  
1,2,3,4-Tetrahydroisoquinoline-3-carboxylic Acids  
(S,S,S configuration) and their In-Vitro  
Angiotensin-Converting Enzyme Inhibitory Activity



R	R <sub>2</sub>	X	Y	Optical Rotation [α] <sub>D</sub> <sup>23</sup>	ACE I Activity (in vitro) IC <sub>50</sub> Molar Conc.
H	Et	H	H	+10.9° (1.0% EtOH) <sup>+</sup>	8.3 × 10 <sup>-9</sup>
H	Et	OCH <sub>3</sub>	OCH <sub>3</sub>	+31.6° (1.0% EtOH) <sup>+</sup>	5.6 × 10 <sup>-9</sup>
H	H	H	H	+14.5° (1.0% MeOH) <sup>+</sup>	2.8 × 10 <sup>-9</sup>
H	H	OCH <sub>3</sub>	OCH <sub>3</sub>	+37.8° (1.0% MeOH) <sup>+</sup>	3.4 × 10 <sup>-9</sup>
PhCH <sub>2</sub>	Et	H	H	-11.7° (1.0% MeOH) <sup>#</sup>	2.0 × 10 <sup>-6</sup>
t-Bu	Et	H	H	+6.4° (2.0% MeOH) <sup>#</sup>	3.2 × 10 <sup>-6</sup>
PhCH <sub>2</sub>	Et	OCH <sub>3</sub>	OCH <sub>3</sub>	+3.4° (1.0% EtOH) <sup>#</sup>	3.0 × 10 <sup>-7</sup>

<sup>+</sup> Hydrochloride Salt

<sup>#</sup> Maleate Salt

The compounds of the invention can be utilized to achieve the reduction of blood pressure by formulating in compositions such as tablets, capsules or elixirs for oral administration or in sterile solutions or suspensions for parenteral administration. About 10 to 500 mg of a compound or mixture of compounds of formula I or physiologically acceptable salt thereof is compounded

with a physiologically acceptable vehicle, carrier, excipient binder, preservative, stabilizer, flavor, etc., in a unit dosage form as called for by accepted pharmaceutical practice. The amount of active substance in these compositions or preparations is such that a suitable dosage in the range indicated is obtained.

Illustrative of the adjuvants which may be incorporated in tablets, capsules and the like are the following: a binder such as gum tragacanth, acacia, corn starch or gelatin; an excipient such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; a sweetening agent such as sucrose, lactose or saccharin; a flavoring agent such as peppermint, oil of wintergreen or cherry. When the dosage unit form is a capsule, it may contain in addition to materials of the above type a liquid carrier such as a fatty oil. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets may be coated with shellac, sugar or both. A syrup or elixir may contain the active compound, sucrose as a sweetening agent, methyl and propyl parabens as preservatives, a dye and a flavoring such as cherry or orange flavor.

Sterile compositions for injection can be formulated according to conventional pharmaceutical practice by dissolving or suspending the active substance in a vehicle such as water for injection, a naturally occurring vegetable oil like sesame oil, coconut oil, peanut oil, cottonseed oil, etc., or a synthetic fatty vehicle like ethyl oleate or the like. Buffers, preservatives, antioxidants and the like can be incorporated as required.

The invention is illustrated by the following examples.

#### EXAMPLE 1

2-[2-[[1-(Ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylic Acid, Hydrochloride, Hydrate (S,S,S).

A quantity of 0.0079 mole of the hydrochloride of 2-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylic acid, phenylmethyl ester (S,S,S) dissolved in 100 ml of tetrahydrofuran was catalytically debenzylated with hydrogen and 0.5 g of 20% Pd/carbon at low pressure. The catalyst was filtered off and the product was precipitated as a relatively nonhydroscopic solid by the addition of a 10 fold quantity of ether; wt 3.7 g (88%); mp 120°-140° C.; tlc (20% MeOH-CHCl<sub>3</sub>/SiO<sub>2</sub>) one spot, R<sub>f</sub> 0.5-0.7;  $[\alpha]_D^{23} = +31.6^\circ$  (1.05% EtOH).

Anal. Calc'd for C<sub>27</sub>H<sub>34</sub>N<sub>2</sub>O<sub>7</sub>·HCl·H<sub>2</sub>O: C, 58.63; H, 6.74; N, 5.07; Found: C, 58.59; H, 6.38; N, 5.06.

The noncrystalline diester hydrochloride starting material used above was prepared by treatment of 5.54 g (0.0079 mole) of the maleate salt (prepared by the process of Example 5) with excess saturated sodium bicarbonate, extraction of the free base into 50% ether-ethyl acetate, treatment of this solution with excess hydrogen chloride and concentration at reduced pressure.

#### EXAMPLE 2

2-[2-[[1-(Ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic Acid, Hydrochloride, Hydrate, (S,S,S).

Procedure A: Debenzylation procedure.

2-[2-[[1-(Ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid, phenylmethyl ester, maleate, (S,S,S) (prepared by the procedure of Example 6) was catalytically debenzylated by the procedure set forth in Example 1 to yield the product; mp 105°-120° C.; yield, 56%; tlc (20% MeOH-CHCl<sub>3</sub>/SiO<sub>2</sub>) one spot R<sub>f</sub> 0.5-0.6;  $[\alpha]_D^{23} = +10.9^\circ$  (1.03% EtOH).

Anal. Calc'd. for C<sub>25</sub>H<sub>30</sub>N<sub>2</sub>O<sub>5</sub>·HCl·H<sub>2</sub>O: C, 60.90; H, 6.75; N, 5.68; Found: C, 61.00; H, 6.37; N, 5.59.

Procedure B: Via cleavage of 1,1-dimethylethyl ester.

A quantity of 100 g of trifluoroacetic acid was added to 11.6 g (0.023 mole) of 2-[2-[[1-ethoxycarbonyl]-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid, 1,1-dimethylethyl ester (S,S,S) (prepared by the procedure of Example 7). The mixture was stirred for one hour at room temperature. Most of the trifluoroacetic acid was removed on the rotary evaporator and the remaining traces were removed by the successive additions and removal by rotary evaporation of 2 × 50 ml of THF. The residual oil was dissolved in about 400 ml of dry ether and the hydrochloride was precipitated by addition of a solution of 1.0 g (excess) of dry hydrogen chloride dissolved in 20 ml of dry ether. After filtration and washing with dry ether, the filter cake was dissolved in about 250 ml of water. This solution was filtered through celite and freeze-dried to obtain the product as a partial hydrate; 10.0 g (90%); mp 113°-120° C.

Anal. Calc'd. for C<sub>25</sub>H<sub>30</sub>N<sub>2</sub>O<sub>5</sub>·HCl· $\frac{1}{2}$  H<sub>2</sub>O: C, 61.55; H, 6.70; N, 5.74; Found: C, 61.51; H, 6.49; N, 5.70.

#### EXAMPLE 3

2-[2-[(1-Carboxy-3-phenylpropyl)amino]-1-oxopropyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylic Acid, Hydrochloride, Hydrate (S,S,S).

A solution of 0.553 g (0.001 mole) of 2-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylic acid, hydrochloride, hydrate (S,S,S) (prepared by the process of Example 1) in 4 ml (0.004 mole) of 1 N sodium hydroxide and 4 ml of methanol was allowed to stand at room temperature for 20 hours. The reaction solution was added to 5 ml of 1 N hydrochloric acid and concentrated at reduced pressure. The last amounts of water were removed by two successive additions and removal at reduced pressure of 25 ml portions of ethanol. The organic portion of the residue was dissolved in 0.5 ml of methanol. Chloroform (30 ml) was added and the solution was dried over sodium sulfate, charcoaled, filtered, and concentrated to give 0.45 g product. This amorphous material was dissolved in 20 ml of tetrahydrofuran and 100 ml of ether was added to precipitate a near white solid product; wt 0.4 g; mp 145°-170° C.; yield, 80%; tlc (20% MeOH-CHCl<sub>3</sub>/SiO<sub>2</sub>) R<sub>f</sub> 0.1;  $[\alpha]_D^{23} = +37.8^\circ$  (1.09% MeOH).

Anal. Calc'd for C<sub>25</sub>H<sub>30</sub>N<sub>2</sub>O<sub>7</sub>·HCl·H<sub>2</sub>O: C, 57.19; H, 6.34; N, 5.34; Found: C, 57.17; H, 6.10; N, 5.51.

## EXAMPLE 4

2-[2-[(1-Carboxy-3-phenylpropyl)amino]-1-oxopropyl]-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic Acid, Hydrochloride, Hemihydrate (S,S,S).

2-[2-[(1-(Ethoxycarbonyl)-3-phenylpropyl)amino]-1-oxopropyl]-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid, hydrochloride, hydrate (S,S,S) was treated by the procedure set forth in Example 3 to yield the product; mp 140°-170° C.; yield, 39%;  $[\alpha]_D^{23} = +14.5^\circ$  (1.08% MeOH).

Anal. Calc'd for  $C_{23}H_{26}N_2O_5 \cdot HCl \cdot \frac{1}{2} H_2O$ : C, 60.59; H, 5.97; N, 6.15; Cl, 7.77; Found: C, 60.68; H, 6.04; N, 5.89; Cl, 7.04.

## EXAMPLE 5

2-[2-[(1-(Ethoxycarbonyl)-3-phenylpropyl)amino]-1-oxopropyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylic Acid, Phenylmethyl Ester, Maleate (S,S,S).

A stirred solution of 5.0 g (0.0158 mole) of ethyl  $\alpha$ -[(1-carboxyethyl)amino]benzenebutanoate hydrochloride (S,S) (prepared by the process of Example 8) in 200 ml of methylene chloride was treated successively with 1.60 g (0.0158 mole) of triethylamine, 2.14 g (0.0158 mole) of 1-hydroxybenzotriazole, 5.16 g (0.0158 mole) of 1,2,3,4-tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylic acid, phenylmethyl ester free base (S-form) (prepared by the process of Example 9); and then with 3.26 g (0.0158 mole) of dicyclohexylcarbodiimide in 10 ml of methylene dichloride. Dicyclohexylurea gradually separated. The mixture was allowed to stand at room temperature overnight. Hexane (300 ml) was added and the urea was filtered. The filtrate was washed with 250 ml of saturated sodium bicarbonate, dried over sodium sulfate and concentrated to remove solvent. The viscous residue was triturated with 50 ml of ether and filtered to remove insolubles. The filtrate was concentrated to give 9.2 g (99%) of crude base.

Preparation of maleate salt: A solution of 9.0 g (0.015 mole) of the above crude base in 50 ml of ethyl acetate was treated with a warm (40° C.) solution of 1.86 g (0.016 mole) of maleic acid in 50 ml of ethyl acetate. White crystals separated; wt 7.2 g (65%); mp 139°-141° C.; tlc of base (generated with aq. sodium bicarbonate treatment of the salt and ethyl acetate extraction) showed one spot, Rf 0.7 (EtOAc/SiO<sub>2</sub>). Recrystallization from ethyl acetate gave pure material of the same mp;  $[\alpha]_D^{23} = +3.4^\circ$  (1.05% EtOH).

Anal. Calc'd for  $C_{34}H_{40}N_2O_7 \cdot C_4H_4O_4$ : C, 64.74; H, 6.29; N, 3.98; Found: C, 64.48; H, 6.30; N, 3.99.

## EXAMPLE 6

2-[2-[(1-(Ethoxycarbonyl)-3-phenylpropyl)amino]-1-oxopropyl]-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic Acid, Phenylmethyl Ester, Maleate (S,S,S).

Ethyl  $\alpha$ -[(1-carboxyethyl)amino]benzenebutanoate hydrochloride (S,S) (prepared by the process of Example 8) was coupled with 1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid, phenylmethyl ester free base (S-form) (prepared by the process of Example 10) by the same procedure used in Example 5; yield, 61%; mp 151°-153° C. (recrystallized from ethyl acetate); tlc of base showed one spot, Rf 0.8 (EtOAc/SiO<sub>2</sub>);  $[\alpha]_D^{23} = -11.7^\circ$  (1.0% MeOH).

Anal. Calc'd for  $C_{33}H_{36}N_2O_5 \cdot C_4H_4O_4$ : C, 67.07; H, 6.25; N, 4.35; Found: C, 66.58; H, 6.09; N, 4.25.

## EXAMPLE 7

2-[2-[(1-Ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic Acid, 1,1-Dimethylethyl Ester (S,S,S).

A mixture of 8.38 g (0.03 mole) of ethyl  $\alpha$ -[(1-carboxyethyl)amino]benzenebutanoate (free amino acid) (S,S) (prepared by the process of Example 8), 8.09 g (0.03 mole) of 1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid, 1,1-dimethylethyl ester hydrochloride (S-form) (prepared by the process of Example 11), 4.05 g (0.03 mole) of 1-hydroxybenzotriazole and 250 ml of THF was cooled in an ice bath to 3°-5° C. With stirring, 3.04 g (0.03 mole) of triethylamine was added, then a solution of 6.92 g (0.0335 mole) of dicyclohexylcarbodiimide in 30 ml of THF was dropped in slowly over 20 minutes. The reaction mixture was stirred at 3°-5° C. for one hour. The ice bath was removed, and the reaction mixture stirred an additional 3 hours. The separated mixture of triethylamine hydrochloride and dicyclohexylurea was removed by filtration and washed with THF. The filtrate was evaporated on the rotary evaporation to remove all volatiles. The resulting gum was dissolved in about 300 ml of ethyl acetate. After filtration through celite the ethyl acetate solution was extracted 2 times with 100 ml of saturated sodium bicarbonate solution, once with 75 ml of 2 N citric acid solution, once with 100 ml of saturated sodium bicarbonate solution and once with 100 ml of saturated sodium chloride solution. After drying with anhydrous MgSO<sub>4</sub> and filtration, the ethyl acetate was removed on the rotary evaporator to yield 16.9 g of a light brown gum. This gum was dissolved in 350 ml of boiling hexane and decanted through celite. The hexane solution was cooled in ice, seeded and stirred until crystallization was well established. The product was filtered, washed with cold hexane and dried; wt 11.6 g (78%); mp 68.5°-71° C.;  $[\alpha]_D^{23} = -12.2^\circ$  (2% MeOH). Pure material had mp 71°-72° C.;  $[\alpha]_D^{23} = -12.6^\circ$  (2% MeOH). The maleate salt had mp 127.5°-128.5° C.;  $[\alpha]_D^{23} = +46.4^\circ$  (2% MeOH).

## EXAMPLE 8

Ethyl  $\alpha$ -[(1-Carboxyethyl)amino]benzenebutanoate Hydrochloride (S,S).

A solution of 2.0 g of t-butyl alanine (S-form) and 3.78 g of ethyl 2-bromo-4-phenylbutanoate in 25 ml of dimethylformamide was treated with 1.8 ml of triethylamine and the solution was heated at 70° C. for 18 hours. The solvent was removed at reduced pressure and the residue was mixed with water and extracted with ethyl ether. The organic layer was washed with water and dried over magnesium sulfate. Concentration of the solvent at reduced pressure gave the oily t-butyl ester of the intermediate which was found to be sufficiently pure by gas liquid chromatography for further use.

A solution of 143.7 g of this t-butyl ester in 630 ml of trifluoroacetic acid was stirred at room temperature for one hour. The solvent was removed at reduced pressure and the residue was dissolved in ethyl ether and again evaporated. This operation was repeated. Then the ether solution was treated dropwise with a solution of hydrogen chloride gas in ethyl ether until precipitation ceased. The solid, collected by filtration, was a mixture

of diastereoisomers, mp 153°-165° C.,  $[\alpha]_{D23} = +3.6^\circ$  (1% MeOH).

In order to separate the preferred, S, S isomer, a suspension of 10.0 g of the mixture in 200 ml of methylene chloride was stirred at room temperature for five minutes and filtered; the solid was washed with additional methylene chloride and finally ether. The solid material, mp 202°-208° C. (dec.),  $[\alpha]_{D23} = -29.3^\circ$  (1% MeOH) was the less preferred diastereoisomer having the R, S configuration (S referring to the portion derived from L-alanine). The preferred S, S diastereoisomer was recovered from the filtrate after concentration and trituration of the residue with ether; mp 137°-139° C.;  $[\alpha]_{D23} = +31.3^\circ$  (1% MeOH).

The free amino acid (S,S-form) was prepared by treatment of an aqueous solution of the hydrochloride with saturated sodium acetate. The product was filtered, washed efficiently with cold water and recrystallized from ethyl acetate; mp 149°-151° C.;  $[\alpha]_{D23} = +29.7^\circ$

(1% 0.1 N HCl).

#### EXAMPLE 9

1,2,3,4-Tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylic Acid, Phenylmethyl Ester, Hydrochloride (S-form).

A mixture of 1,2,3,4-tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylic acid, hydrochloride (S-form) and 600 ml of benzyl alcohol was saturated with hydrogen chloride gas. The temperature rose to 45° C. The mixture was stirred at room temperature for three days. A relatively small amount of solid was filtered off and the filtrate was treated with ca 2-liters of ether to precipitate crude product; wt 37.5 g; yield, 83%. Purification was effected by treatment with excess saturated sodium bicarbonate, extraction of base into ethyl acetate and precipitation of hydrochloride salt with HCl gas. Recrystallization from methanol-ether gave pure product; mp 255°-260° C.;  $[\alpha]_{D23} = -81.3^\circ$  (1.0% MeOH); tlc (20% MeOH-CHCl<sub>3</sub>:SiO<sub>2</sub>) one spot R<sub>f</sub> 0.8.

Anal. Calc'd for C<sub>19</sub>H<sub>21</sub>NO<sub>4</sub>.HCl: C, 62.72; H, 6.10; N, 3.85; Found: C, 62.54; H, 5.99; N, 4.00.

#### EXAMPLE 10

1,2,3,4-Tetrahydro-3-isoquinolinecarboxylic Acid, Phenylmethyl Ester, Hydrochloride (S-form).

Benzyl alcohol, 750 ml, was treated with 150 g of commercial polyphosphoric acid and warmed and stirred at 90° C. to obtain a homogeneous mixture. Solid 1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid (S-form) 165.2 g was added. The mixture was stirred 4 hours at 95°-105° C. and then allowed to stand at room temperature for 18 hours. A solution of 18.5 g gaseous hydrochloric acid in 2.5 l of anhydrous ether was added, and the product separated slowly on cooling overnight. Filtration gave the crude benzyl 1,2,3,4-tetrahydro-3-isoquinoline carboxylate hydrochloride. This was purified by recrystallization from ethanol twice to give material with mp 190.5°-191° C.;  $[\alpha]_{D23} = -83.3^\circ$  (1% 1:1 methanol/1 N hydrochloric acid).

#### EXAMPLE 11

1,2,3,4-Tetrahydro-3-isoquinolinecarboxylic Acid, 1,1-Dimethylethyl Ester Hydrochloride (S-form).

This compound was prepared by passing 447 g of isobutylene into a 0° C. solution of 63.5 g of 1,2,3,4-tetrahydro-3-isoquinoline carboxylic acid (S-form) in 650

ml of dry dioxane and 65 ml of concentrated sulfuric acid under nitrogen. The reaction vessel was sealed and shaken for 17 hours at room temperature. The reaction vessel was vented and the mixture was poured into 25 l of cold 2 N sodium hydroxide. The produce is extracted into ether. The ether solution was washed with water, dried, and concentrated to about 500 ml. This was treated with excess 6 N isopropanolic hydrochloric acid to precipitate the product, which was collected by filtration. A sample purified by recrystallization from ethanol/ether had mp 190°-192° C. (dec.),  $[\alpha]_{D23} = -88.7^\circ$  (2% MeOH).

#### EXAMPLE 12

A quantity of 1000 tablets each containing 100 mg of 2-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylic acid, hydrochloride, hydrate (S,S,S) is produced from the following ingredients:

2-[2-[[1-(Ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-Tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylic acid, hydrochloride hydrate (S,S,S)	100	g
Corn starch	50	g
Gelatin	7.5	g
Avicel (microcrystalline cellulose)	25	g
Magnesium stearate	2.5	g

2-[2-[[1-(Ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylic acid, hydrochloride, hydrate (S,S,S) and corn starch are admixed with an aqueous solution of the gelatin. The mixture is dried and ground to fine powder. The Avicel and then the magnesium stearate are admixed with the granulation. This is then compressed in a tablet press to form 1000 tablets each containing 100 mg of active ingredients.

#### EXAMPLE 13

A quantity of 1000 tablets each containing 200 mg of 2-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylic acid, hydrochloride, hydrate (S,S,S) is produced from the following ingredients:

2-[2-[[1-(Ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylic acid, hydrochloride, hydrate (S,S,S)	200	g
Lactose	100	g
Avicel	150	g
Corn starch	50	g
Magnesium stearate	5	g

The 2-[2-[[1-(Ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylic acid, hydrochloride, hydrate (S,S,S) lactose and Avicel are admixed, then blended with the corn starch. Magnesium stearate is added. The dry mixture is compressed in a tablet press to form 1000, 505 mg tablets each containing 200 mg of active ingredient. The tablets are coated with a solution of Methocel E 15 (methyl cellulose) including as a color a lake containing yellow No. 6.

## EXAMPLE 14

Two piece No. 1 gelatin capsules each containing 250 mg of 2-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylic acid, hydrochloride, hydrate (S,S,S) are filled with a mixture of the following ingredients:

2-[2-[[1-(Ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylic acid, hydrochloride, hydrate (S,S,S)	250 g
Magnesium stearate	7 g
USP lactose	193 mg

## EXAMPLE 15

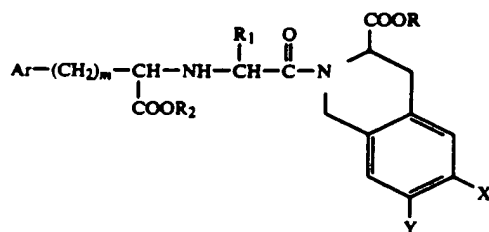
An injectable solution is produced as follows:

2-[2-[[1-(Ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylic acid, hydrochloride, hydrate (S,S,S)	500 g
Methyl paraben	5 g
Propyl paraben	1 g
Sodium chloride	25 g
Water for injection q.s.	5 l

The active substance, preservatives and sodium chloride are dissolved in 3 liters of water for injection and then the volume is brought up to 5 liters. The solution is filtered through a sterile filter and aseptically filled into presterilized vials which are then closed with presterilized rubber closures. Each vial contains 5 ml of solution in a concentration of 100 mg of active ingredient per ml of solution for injection.

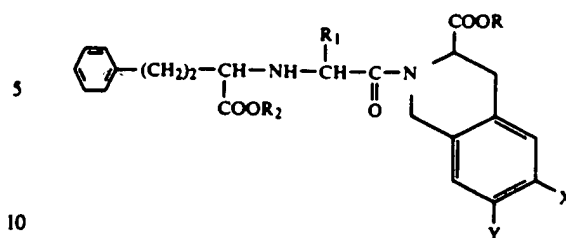
We claim:

1. A substituted acyl compound of 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid having the formula



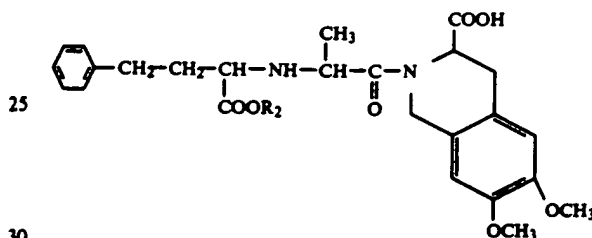
where R is hydrogen, lower alkyl or phenylalkyl; R<sub>1</sub> is hydrogen, lower alkyl, or benzyl; R<sub>2</sub> is hydrogen, or lower alkyl and Ar is phenyl, or substituted phenyl having 1 or 2 substituents selected from the group consisting of fluorine, chlorine, bromine, lower alkyl, lower alkoxy, hydroxy or amino; X and Y are independently hydrogen, lower alkyl, lower alkoxy, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, hydroxy, or X and Y together are methylenedioxy; and m is 0 to 3; wherein lower alkyl, alkyl in the group phenylalkyl; and lower alkoxy has 1 to 4 straight or branched carbon atoms and the pharmaceutically acceptable salts thereof.

2. A substituted acyl compound of 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid according to claim 1 having the formula



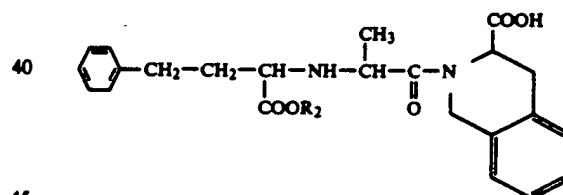
where R is hydrogen, t-butyl, or benzyl; R<sub>1</sub> is hydrogen or lower alkyl; R<sub>2</sub> is hydrogen, methyl or ethyl; X and Y are independently hydrogen, lower alkyl, hydroxy or lower alkoxy; and the pharmaceutically acceptable salts thereof.

3. A substituted acyl compound of 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid according to claim 2 having the formula



where R<sub>2</sub> is hydrogen, methyl or ethyl and the pharmaceutically acceptable salts thereof.

4. A substituted acyl compound of 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid according to claim 2 having the formula



where R<sub>2</sub> is hydrogen, methyl or ethyl and the pharmaceutically acceptable salts thereof.

5. The compound according to claim 2 which is 2-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylic acid, phenylmethyl ester, maleate (S,S,S).

6. The compound according to claim 2 which is 2-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-3-isoquinoline-carboxylic acid, phenylmethyl ester, maleate (S,S,S).

7. The compound according to claim 2 which is 2-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid, 1,1-dimethylethyl ester, (S,S,S).

8. The compound according to claim 3 which is 2-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylic acid, hydrochloride, hydrate (S,S,S).

9. The compound according to claim 3 which is 2-[2-[[1-carboxy-3-phenylpropyl]amino]-1-oxopropyl]-

1,2,3,4-tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylic acid, hydrochloride, hydrate (S,S,S).

10. The compound according to claim 4 which is 2-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid, hydrochloride, hydrate (S,S,S).

11. The compound according to claim 4 which is 2-[2-[[1-(1-carboxy-3-phenylpropyl)amino]-1-oxopropyl]-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid, hydrochloride, hemihydrate (S,S,S).

12. The compound according to claim 3 which is 2-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-3-isoquinoline carboxylic acid, hydrochloride, (S,S,S).

13. The compound according to claim 4 which is 2-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-3-isoquinoline carboxylic acid, hydrochloride (S,S,S).

14. A pharmaceutical composition comprising 10 to 500 mg of a substituted acyl compound of a 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid or a mixture of compounds according to claim 1 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

15. A method of treating hypertension by administering an effective amount of a substituted acyl compound of 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid according to claim 1 or a pharmaceutically acceptable salt thereof.

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bcc: Dr. R. A. Buchanan  
Dr. R. M. Hodges  
Dr. H. R. Kaplan\*  
Dr. J. R. Latts  
Dr. J. G. Toole  
Regulatory Affairs, MP\*  
✓IND File, AA\*

\* with attachment

IND \_\_\_\_\_  
CI-906 Hydrochloride Capsules  
Ref. No. 906/1  
Submitted: MAY 17 1982

The Secretary of Health and Human Services  
For the Commissioner of Food and Drugs  
5600 Fishers Lane  
Rockville, Maryland 20857

Dear Sir:

Attached is our Notice of Claimed Investigational Exemption for CI-906 hydrochloride to clinically evaluate this angiotensin converting enzyme (ACE) inhibitor.

Please note in Item 10 of this Notice that the clinical pharmacology study to be conducted by our Dr. J. R. Latts and Dr. J. R. Goulet under Protocol 906-2 will utilize this compound as a solution. The purpose of using the drug in solution for this study is to obtain maximum absorption and consequently better pharmacokinetic data. Protocol 906-3, to be conducted by Dr. H. Gavras, and subsequent clinical studies will use the capsule formulations described under Items 2 and 3 of this Notice.

Very truly yours,

Original signed by  
T. N. T. Olson

T. N. T. Olson, Ph.D.  
Director  
Regulatory Liaison and Compliance

TNTO-JEM:lmd

Attachment (Volumes 1-6)

In triplicate



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville MD 20857

MAY 27 1982

IND FILE  
COPY  
MEDICAL AFFAIRS

IND 20,336

Warner-Lambert Company  
Pharmaceutical Research Division  
2800 Plymouth Road  
Ann Arbor, Michigan  
48105

Dear Sir/Madam: Dr. Olson

We are pleased to acknowledge receipt of your Notice of Claimed Investigational Exemption for a New Drug (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act. Please note the following identifying data:

IND Number Assigned: 20,336  
Sponsor: Warner Lambert  
Name of Drug: CI-906 Hydrochloride Capsules  
Date of Submission: May 17, 1982  
Date of Receipt: May 19, 1982

IT IS UNDERSTOOD THAT STUDIES IN HUMANS WILL NOT BE INITIATED UNTIL 30 DAYS AFTER THE DATE OF RECEIPT SHOWN ABOVE. If, within the 30 day period, we notify you of serious deficiencies that require correction before human studies can begin or that would require restriction of human studies until correction, it is understood that you will continue to withhold or restrict such studies until you are notified that the material you have submitted to correct the deficiencies is satisfactory.

You are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and Regulations. This responsibility includes the immediate reporting of any alarming reactions in either animal or human studies, and submission of progress reports at intervals not to exceed one year.

cc: Regulatory Affairs, M.P.

RECEIVED

JUN 3 1982

IND

20, 336

Page 2

As Sponsor of the clinical study proposed in this IND, you are now free to obtain supplies of the investigational drug.

The 30-day restriction does not apply if the IND number was assigned for the emergency use of the drug in one patient only.

Should you have any questions concerning this IND, please call:

*Ms. Jacqueline Knight*

Consumer Safety Officer

(301) 443-

*4730*

Please forward all future communications concerning this IND in TRIPLICATE IDENTIFIED with this IND NUMBER and addressed as follows:

Food and Drug Administration  
Bureau of Drugs, HFD-110  
Attention: DOCUMENT CONTROL ROOM # 16B-30  
5600 Fishers Lane  
Rockville, Maryland 20857

Sincerely yours,

*Natella A. Morgenstern*  
Natella A. Morgenstern

Supervisory Consumer Safety Officer  
Division of Cardio-Renal  
Drug Products  
Bureau of Drugs

CC:

Orig. File - pink

Division File - yellow

Division CSO - blue

ACKNOWLEDGEMENT

FORM FDA 3228b (1/82)

# PARKE-DAVIS

Pharmaceutical Research Division

Warner-Lambert Company

NDA 19-885  
Quinapril Hydrochloride  
Tablets

January 26, 1989

Raymond J. Lipicky, M.D.  
Director  
Division of Cardio-Renal  
Drug Products (HFD-110)  
U.S. Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857

Dear Dr. Lipicky:

We are providing a new drug application for quinapril hydrochloride tablets for treatment of patients with hypertension. The tablets will be provided in strengths of 5 mg, 10 mg, 20 mg and 40 mg.

The patent information required by 21 U.S.C. 355(b)(1) is provided in section 13 of this NDA. In addition, this section documents that quinapril tablets for hypertension meet the requirements of 21 U.S.C. 355(j)(4)(D)(ii) and 355(c)(3)(D)(ii) for a five year market exclusivity period. A copy of section 13 immediately follows. A copy of this same information will also be forwarded shortly to FDA's Division of Information Resources.

A request for waiver of the requirement for in vivo bioavailability data on the 10 mg and 20 mg tablet strengths is made in the Human Pharmacokinetics and Bioavailability section. Documentation that these two strengths meet the requirements for granting a waiver are provided in Volume 39, page 06 000131.

On July 8, 1988 Parke-Davis representatives met with Dr. Wolters and Ms Danute Cunningham to address Chemistry, Manufacturing and Controls issues in this NDA. Minutes of this meeting were provided to IND 20,336 on August 10, 1988 (serial Number 471). At this meeting it was agreed that Parke-Davis would respond in the NDA to two letters from FDA dated July 1, 1988 and March 2, 1988. These responses are provided in the Chemistry, Manufacturing & Controls Section, beginning in Volume 3, page 03 000277.

Parke-Davis representatives also met twice with FDA on the clinical development of quinapril hydrochloride. On February 12, 1986, we met to review Phase 2 results and discuss the upcoming Phase 3 program. Parke-Davis' minutes of this meeting were provided to IND 20,336 on March 4, 1986 (serial number 167).

On May 9, 1988, a pre-NDA meeting was held with FDA. FDA suggestions made at this meeting and at a follow-up telephone conference have been incorporated in the NDA presentation. Minutes of the pre-NDA meeting and the follow-up telephone conference were provided to IND 20,336 on May 27, 1988 (serial number 463) and on July 19, 1988 (serial number 468), respectively.

While this NDA is for hypertension, quinapril has also been studied for treatment of patients with congestive heart failure (CHF). At the May 9, 1988 pre-NDA meeting FDA recommended not addressing CHF efficacy in the NDA. Therefore, CHF has not been addressed in the Integrated Summary of Efficacy. However, we have included CHF patients in the safety analyses, and reports of completed CHF studies have been included in the Clinical Data section.

Parke-Davis will test the stability of at least the first three lots of each strength of tablet in each package according to the stability testing protocol provided in Section 3, Volume 3, page 03 000095 of this application. In addition, the first three lots packaged at each packaging facility in this application will be tested according to this protocol.

Sincerely,

A handwritten signature in cursive script that reads "Jon Villaume". The signature is written in dark ink and is positioned above the printed name and title.

Jon Villaume  
Director  
Regulatory Affairs

REGULATORY LIAISON AND COMPLIANCE  
INFORMATION MANAGEMENT SYSTEM

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CI NUMBER= 906 APPL NUMBER= 20,336

DOC DATE SER/SUPPL NO TITLE

17-MAY-82 1 INITIAL IND  
CONTENT:

VOLUMES=6

ITEM 1: DRUG NAME, STRUCTURE AND METHOD OF  
ADMINISTRATION.

ITEM 2: DRUG COMPONENTS OF THE FORMULATED DRUG.

ITEM 3: QUANTITATIVE COMPOSITION OF THE FORMULATED  
DRUG.

ITEM 4: DRUG SOURCE AND PREPARATIONS OF THE NEW  
DRUG SUBSTANCE.

ITEM 5: MANUFACTURING METHODS, FACILITIES, AND  
CONTROLS FOR THE FORMULATED DRUG.

ITEM 6: PRECLINICAL AND OTHER PERTINENT  
BACKGROUND INFORMATION

ITEM 7: INFORMATIONAL MATERIAL TO BE SUPPLIED  
INVESTIGATORS AND DRUG LABEL.

ITEM 8: COMPANY REQUIREMENTS FOR CLINICAL  
INVESTIGATORS

ITEM 9: NAME AND QUALIFICATIONS OF THE MONITORS  
AND INVESTIGATORS.

ITEM 10: PROPOSED CLINICAL INVESTIGATIONS.

27-MAY-82 LETTER FROM FDA ACKNOWLEDGING RECEIPT (IND 20,336)  
CONTENT:

LETTER FROM: FDA

RE: ACKNOWLEDGEMENT OF RECEIPT OF IND ON  
19-MAY-82; NUMBER 20,336 ASSIGNED.

21-JUN-82 2 INFORMATION AMENDMENT  
CONTENT:

REVISED PAGE  
PG. 9

14-JUL-82 3 INFORMATION AMENDMENT  
CONTENT:

REVISED PAGES FOR PR. 906-2  
PGS. 1, 2, 3, 7

28-JUL-82 4 INFORMATION AMENDMENT  
CONTENT:

REVISED PAGE RR X-740-00937  
PG. 7

23-AUG-82 5 INFORMATION AMENDMENT  
CONTENT:

REVISED PAGES FOR PR. 906-3  
COMPLETE PROTOCOL  
DATE: 12-JUN-82

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CI NUMBER= 906 APPL NUMBER= 20,336

DOC DATE	SER/SUPPL NO	TITLE
20-DEC-82	12	PR. 906-5
CONTENT:		PR. 906-5 (J.R. LATTS & J.R. GOULET)
06-JAN-83	13	INFORMATION AMENDMENT
CONTENT:		RR 745-00541 AUTHOR: ANDERSON, J.A. ET AL DATE: 9-DEC-82 "TERATOLOGY STUDY IN RATS WITH CI-906"
06-JAN-83	14	INFORMATION AMENDMENT
CONTENT:		RR 745-00539 AUTHOR: ANDERSON, J.A. ET AL DATE: 20-DEC-82 "13-WEEK ORAL TOXICITY STUDY OF CI-906 IN BEAGLE DOGS"
24-JAN-83	15	INFORMATION AMENDMENT
CONTENT:		REVISED PAGES FOR PR. 906-5 COMPLETE PROTOCOL DATE: 3-JAN-83
28-JAN-83	16	INFORMATION AMENDMENT
CONTENT:		RR 745-00552 AUTHOR: KIM, S.N. ET AL DATE: 29-DEC-82 "THIRTEEN-WEEK ORAL TOXICITY STUDY OF CI-906 IN MALE AND FEMALE ALBINO RATS"
23-FEB-83	17	INFORMATION AMENDMENT
CONTENT:		RR 724-00028 AUTHOR: PEARSE, S.B. DATE: 18-FEB-83 "A STUDY OF THE EFFECTS OF CI-906, AN INHIBITOR OF ANGIOTENSIN CONVERTING ENZYME, ON THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM AND RELATED CARDIOVASCULAR RESPONSES AFTER ANGIOTENSIN-1 CHALLENGE. PART 1: DOSE-RANGING STUDY IN TWO HEALTHY MEN. PART 2: DURATION OF ACTION STUDY IN FIVE HEALTHY MEN. (PR. 906-1, P.197)"

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CI NUMBER= 906 APPL NUMBER= 20,336

DOC DATE	SER/SUPPL NO	TITLE
25-MAR-83 CONTENT:	18	INFORMATION AMENDMENT RR 250-01303 AUTHOR: BARSOUM, N.J. ET AL DATE: 15-MAR-83 "ACUTE ORAL TOXICITY STUDY OF CI-906 (PD 109452-2) IN MICE"
14-APR-83 CONTENT:	19	ANNUAL REPORT ISSUE DATE: 14-APR-83
07-JUN-83	20	PR. 906-6
07-JUN-83	21	PR. 906-8
01-JUL-83 CONTENT:	22	INFORMATION AMENDMENT RR 745-00608 AUTHOR: ANDERSON, J.A. ET AL DATE: 20-JUN-83 "EXPLORATORY RANGE-FINDING TERATOLOGY STUDY IN RABBITS WITH CI-906"
01-SEP-83 CONTENT:	23	INFORMATION AMENDMENT RR 250-01332 AUTHOR: BARSOUM, N.J. ET AL DATE: 26-AUG-83 "ACUTE ORAL TOXICITY STUDY OF CI-906 (PD109452-2) IN MICE"
27-SEP-83	24	PR. 906-10
19-OCT-83 CONTENT:	25	INFORMATION AMENDMENT RR 745-00639 AUTHOR: ANDERSON, J.A. ET AL DATE: 11-OCT-83 "TERATOLOGY STUDY IN RABBITS (CI-906)"
22-NOV-83 CONTENT:	26	INFORMATION AMENDMENT REVISED PAGE RR 745-00639 PG. 2 DATE" 18-NOV-83 CROSS REFERENCE: SERIAL #25



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CI NUMBER= 906 APPL NUMBER= 20,336

DOC DATE	SER/SUPPL NO	TITLE
28-DEC-83 CONTENT:	27	INFORMATION AMENDMENT RR 250-01338 AUTHOR: BARSOUM, N.J. ET AL DATE: 2-DEC-83 "14 DAY REPEATED DOSE ORAL TOXICITY STUDY OF CI-906 IN MICE"
11-JAN-84	28	PR. 906-7
11-JAN-84	29	PR. 906-9
31-JAN-84 CONTENT:	30	INFORMATION AMENDMENT RR MEMO-939-0143 AUTHOR: SHAH, M. DATE: 23-JAN-84 "REVISED HPLC ASSAY OF CI-906 (ACE INHIBITOR) CAPSULES" CROSS REFERENCE: SERIAL #10
17-FEB-84 CONTENT:	31	SAFETY REPORT PATIENT NO.: 5 (TJP) PR. 906-6 AE: EXPERIENCED FACIAL SWELLING AND LARYNGEAL EDEMA WITH BREATHING DIFFICULTY. DRUG RELATED.
02-MAR-84 CONTENT:	32	INFORMATION AMENDMENT RR 740-01319 AUTHOR: WILEY, J.N. ET AL DATE: 9-FEB-84 "EVALUATION OF CI-906, CI-907, AND CI-925, POTENTIAL ACE INHIBITORS, AND REFERENCE DRUGS CAPTOPRIL AND ENALAPRIL IN THE MOUSE ANTIWRITHING TEST"
13-MAR-84 CONTENT:	33	SAFETY REPORT PATIENT NO.: 5 (TJP) PR. 906-6 AE: EXPERIENCED FACIAL SWELLING AND LARYNGEAL EDEMA WITH BREATHING DIFFICULTY. DRUG RELATED. FOLLOW-UP REPORT - SERIAL #31

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16-MAR-84 34 ANNUAL REPORT

CONTENT: ISSUE DATE: 16-MARCH-84

16-MAR-84 35 INFORMATION AMENDMENT

CONTENT: RR 764-00188  
AUTHOR: BORONDY, P.E. ET AL  
DATE: 28-FEB-84  
"CI-906-14C: METABOLIC DISPOSITION STUDIES IN RATS  
AND MONKEYS, STABILITY TO DEESTERIFICATION AND  
ACE INHIBITION IN VITRO"

29-MAR-84 36 SAFETY REPORT

CONTENT: PATIENT NO.: 2 (RF)  
PR. 906-7  
AE: DEATH DUE TO PATIENT'S ADVANCE CARDIAC  
DISEASE.  
NOT DRUG RELATED.

12-APR-84 37 INFORMATION AMENDMENT

CONTENT: REVISED PAGES RR 740-00942  
COMPLETE REPORT  
DATE: 16-APR-82

12-APR-84 38 INFORMATION AMENDMENT

CONTENT: RR 724-00036  
AUTHOR: LATTS, J.R. ET AL  
DATE: 23-MAY-84  
"A CLINICAL PHARMACOLOGIC STUDY OF CI-906 HCL  
SOLUTION, PROTOCOL 906-2"  
  
RR MEMO-764-00156  
AUTHOR: GRYCZKO C. ET AL  
DATE: 30-NOV-83  
"ACE INHIBITOR LEVELS IN PLASMA FOLLOWING PERORAL  
ADMINISTRATION OF CI-906 TO NORMAL HUMAN  
VOLUNTEERS. PROTOCOL 906-2"

12-APR-84 38 INFORMATION AMENDMENT - CONTINUED

CONTENT: RR MEMO-764-00131  
AUTHORS: BORONDY, P.E.  
EASTON, M.L.  
DATE: 6-JUN-83  
"INHIBITION OF PLASMA ANGIOTENSIN CONVERTING  
ENZYME (ACE) ACTIVITY FOLLOWING PERORAL  
ADMINISTRATION OF CI-906 TO NORMAL HUMAN  
VOLUNTEERS. PROTOCOL CI-906-2"

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INFORMATION MANAGEMENT SYSTEM

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CI NUMBER= 906 APPL NUMBER= 20,336

DOC DATE	SER/SUPPL NO	TITLE
23-APR-84 CONTENT:		LETTER RE: FDA REQUEST FOR INFORMATION  LETTER FROM: LIPICKY, R.J., M.D. RE: TERATOLOGY STUDIES IN RABBITS.
30-APR-84 CONTENT:	39	INFORMATION AMENDMENT  RR 745-00686 AUTHOR: ANDERSON, J.A. ET AL DATE: 16-APR-84 "52-WEEK ORAL TOXICITY STUDY AND 104-WEEK CARCINOGEN BIOASSAY OF CI-906 IN RATS - 26-WEEK SUMMARY REPORT"
10-MAY-84 CONTENT:	40	SAFETY REPORT  PATIENT NO.: 2 (RF) PR. 906-9 AE: DEATH DUE TO PATIENT'S ADVANCE CARDIAC DISEASE. NOT DRUG RELATED. WE WERE INADVERTENTLY ADVISED THAT THIS PATIENT WAS ENROLLED IN PR. 906-7. FOLLOW-UP REPORT - SERIAL #36
11-MAY-84 CONTENT:	41	IB UPDATE  DATE: 24-APR-84 RR X-720-00952 AUTHOR: BAUKEMA, J. ET AL "INVESTIGATOR'S BRONCHURE - 906"
11-MAY-84 CONTENT:	42	INFORMATION AMENDMENT  RR 740-01372 AUTHORS: GERMAIN, C.L. MERTZ, T.E. "COMPARISON OF THE EFFECTS OF CI-906, CAPTOPRIL AND ENALAPRIL (ACE INHIBITORS) ON THE BLOOD PRESSURE AND HEART RATE RESPONSES TO BRADYKININ BEFORE AND AFTER TREATMENT WITH INDOMETHACIN IN CONSCIOUS RABBITS"
11-MAY-84	43	PR. 906-20

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DOC DATE	SER/SUPPL NO	TITLE
14-MAY-84 CONTENT:	44	LETTER RE: RESPONSE TO REQUEST FOR INFORMATION LETTER TO: LIPICKY, RAYMOND J., M.D. RE: RESPONSE TO 23-APR-84 LETTER REQUESTING ADDITIONAL TERATOLOGY INFORMATION IN RABBITS. MEMO FROM DR. F.A. DE LA IGLESIA
18-MAY-84	45	PR. 906-14
18-MAY-84	46	PR. 906-17
18-MAY-84	47	PR. 906-18
18-MAY-84	48	PR. 906-19
18-MAY-84	49	PR. 906-22
18-MAY-84 CONTENT:	50	INFORMATION AMENDMENT RR: 745-00716 AUTHOR: JAYASEKARA, M.U. ET AL DATE: 14-MAY-84 "52-WEEK ORAL TOXICITY STUDY OF CI-906 IN BEAGLE DOGS - 26-WEEK SUMMARY REPORT"
31-MAY-84	51	PR. 906-15
07-JUN-84	52	PR. 906-26
07-JUN-84	53	PR. 906-13
07-JUN-84	54	PR. 906-21
07-JUN-84 CONTENT:	55	PROTOCOL AMENDMENT AMENDMENT NO. 1 PR. 906-9 DATE: 16-MAY-84 PROVIDES EXTENDED TREATMENT FOR PATIENTS RESPONDING TO CI-906 CAPSULE THERAPY.

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DOC DATE	SER/SUPPL NO	TITLE
14-JUN-84	56	INFORMATION AMENDMENT
CONTENT: REVISED PAGES 745-00686 PGS. 15, 49, 50, 51, 52 DATE: 6-JUN-84 CROSS REFERENCE: SERIAL #39		
14-JUN-84	57	LETTER RE: PROTOCOL CANCELLATION
CONTENT: LETTER TO: LIPICKY, RAYMOND J., M.D. PR. 906-26 RE: CANCELLATION OF PROTOCOL.		
05-JUL-84	58	PR. 906-16
12-JUL-84	59	PR. 906-12
09-AUG-84	60	INFORMATION AMENDMENT
CONTENT: RR 724-00034 AUTHOR: LATTS, J.R. ET AL DATE: 3-AUG-84 "REPORT OF A DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF THE PHARMACOKINETICS AND TOLERANCE OF CI-906 HCL IN NORMAL HEALTHY SUBJECTS (PROTOCOL 906-5)"		
09-AUG-84	61	LETTER RE: PROTOCOL CANCELLATION
CONTENT: LETTER: LIPICKY, RAYMOND J., M.D. PRS. 906-6, 10 RE: CANCELLATION OF PROTOCOL		
07-SEP-84	62	PROTOCOL AMENDMENT
CONTENT: AMENDMENT NO. 1 PR. 906-19 DATE: 31-AUG-84 PROVIDES FOR LONG-TERM, OPEN-LABEL TREATMENT WITH CI-906, 40.0 MG/DAY FOR PATIENTS.		
07-SEP-84	63	INFORMATION AMENDMENT
CONTENT: REVISED PAGE 745-00541 PG. 2 DATE: 28-AUG-84 CROSS REFERENCE: SERIAL #13		

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DOC DATE	SER/SUPPL NO	TITLE
21-SEP-84	64	INFORMATION AMENDMENT
CONTENT:		
RR: 764-00268		
AUTHORS: JORDAN, R.A.		
CHANG, T.		
DATE: 27-AUG-84		
"THE EFFECT OF REPEATED ADMINISTRATION OF CI-906 ON THE RAT LIVER MICROSOMAL DRUG METABOLISM PARAMETERS"		
21-SEP-84	65	PROTOCOL AMENDMENT
CONTENT:		
AMENDMENT NO. 1		
PRS. 906-12, 16, 17, 20, 21		
DATE: 31-AUG-84		
PROVIDES FOR FURTHER TREATMENT WITH CI-906, 40.0 MG/DAY, ON AN OPEN-LABEL BASIS FOR PATIENTS.		
09-OCT-84	66	PROTOCOL AMENDMENT
CONTENT:		
AMENDMENT NO. 1		
PR. 906-22		
DATE: 31-AUG-84		
PROVIDES FOR FURTHER TREATMENT WITH CI-906, 40.0 MG/DAY, ON AN OPEN-LABEL BASIS FOR PATIENTS.		
09-OCT-84	67	INFORMATION AMENDMENT
CONTENT:		
RR 745-00749		
AUTHOR: ANDERSON, J.A. ET AL		
DATE: 17-SEP-84		
"FERTILITY AND REPRODUCTION STUDIES IN RATS WITH CI-906"		
24-OCT-84	68	PROTOCOL AMENDMENT
CONTENT:		
AMENDMENT NO. 1		
PR. 906-15		
DATE: 31-AUG-84		
PROVIDES FOR FURTHER OPEN-LABEL TREATMENT WITH CI-906, 40.0 MG/DAY FOR PATIENTS.		
06-NOV-84	69	INFORMATION AMENDMENT
CONTENT:		
RR 724-00039		
AUTHOR: GOULET, J.R. ET AL		
DATE: 24-OCT-84		
"REPORT OF A STUDY TO DETERMINE THE EFFECTIVE DOSE AND SAFETY OF CI-906 HCL IN PATIENTS WITH MILD TO MODERATE UNCOMPLICATED HYPERTENSION (PROTOCOL 906-4)"		

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DOC DATE	SER/SUPPL NO	TITLE
20-NOV-84 CONTENT:	70	PROTOCOL AMENDMENT  AMENDMENT NO. 2 PR. 906-19 DATE: 1-NOV-84 PROVIDES FOR LONG-TERM, OPEN-LABEL TREATMENT WITH CI-906, 80.0 MG/DAY FOR PATIENTS.
17-DEC-84 CONTENT:	71	PROTOCOL AMENDMENT  AMENDMENT NO. 1 PR. 906-7 INCREASES THE TOTAL NUMBER OF PATIENTS TO BE TREATED FROM 12 TO 20 PATIENTS.  AMENDMENT NO. 2 PR. 906-9 INCREASES THE TOTAL NUMBER OF PATIENTS TO BE TREATED FROM 12 TO 20 PATIENTS.
26-DEC-84 CONTENT:	72	INFORMATION AMENDMENT  RR 745-00776 AUTHOR: ANDERSON, J.A. ET AL DATE: 18-DEC-84 "52-WEEK ORAL TOXICITY STUDY AND 104-WEEK CARCINOGEN BIOASSAY OF CI-906 IN RATS - 52-WEEK SUMMARY REPORT"
26-DEC-84 CONTENT:	73	INFORMATION AMENDMENT  RR 745-00767 AUTHOR: JAYASEKARA, M.U. DATE: 18-DEC-84 "52-WEEK ORAL TOXICITY STUDY OF CI-906 IN BEAGLE DOGS"
10-JAN-85	74	PR. 906-31
10-JAN-85	75	PR. 906-33
10-JAN-85	76	PR. 906-33
10-JAN-85	77	PR. 906-36

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10-JAN-85	78	PR. 906-44
10-JAN-85	79	PR. 906-27
10-JAN-85	80	PR. 906-28
10-JAN-85 CONTENT:	81	INFORMATION AMENDMENT RR 745-00779 AUTHOR: JAYASEKARA, M.U. ET AL DATE: 5-DEC-84 "THIRTEEN-WEEK MOUSE ORAL RANGE FINDING STUDY: CI-906"
17-JAN-85	82	PR. 906-11 (P.215)
17-JAN-85	83	PR. 906-48 (MUN/654)
17-JAN-85	84	PR. 906-49 (MUN/656)
17-JAN-85	85	PR. 906-52 (MUN/652)
17-JAN-85	86	PR. 906-53 (MUN/657)
17-JAN-85	87	PR. 906-54 (MUN/655)
17-JAN-85	88	PR. 906-35
17-JAN-85	89	PR. 906-43
17-JAN-85	90	PR. 906-46
31-JAN-85	91	PR. 906-41
31-JAN-85 CONTENT:	92	INFORMATION AMENDMENT AMENDMENT NO. 2 PR. 906-20 DATE: 1-NOV-84 PROVIDES FOR THE USE OF CI-906 80 MG/DAY ON AN OPEN-LABEL BASIS FOR PATIENTS WHO HAVE COMPLETED THE DOUBLE-BLIND PORTION OF THE STUDY.



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DOC DATE	SER/SUPPL NO	TITLE
31-JAN-85	93	INFORMATION AMENDMENT
CONTENT: RR 724-00041 AUTHORS: LATTS, J.R. GOULET, J.R. DATE: 1-JAN-85 "REPORT OF A STUDY TO DETERMINE THE SAFETY AND MINIMUM ANTI-HYPERTENSIVE DOSE OF CI-906 HCL (PROTOCOL 906-3)"		
07-FEB-85	94	PR. 906-55 (MUN/658)
07-FEB-85	95	PR. 906-56 (PAR/32)
07-FEB-85	96	PR. 906-37
14-FEB-85	97	ANNUAL REPORT
CONTENT: ISSUED DATE: 14-FEB-85		
14-FEB-85	98	PROTOCOL AMENDMENT
CONTENT: AMENDMENT NO. 3 PR. 906-19 DATE: 15-NOV-84 PROVIDES FOR THE USE OF CI-906 CAPSULES, 60 MG/DAY ON AN OPEN-LABEL BASIS FOR PATIENTS WHO HAVE COMPLETED THE DOUBLE-BLIND POSTION		
14-FEB-85	99	INFORMATION AMENDMENT
CONTENT: RR MEMO-764-00303 AUTHOR: GRYCZKO, C. ET AL DATE: 18-DEC-84 "ACE INHIBITOR LEVELS IN PLASMA FOLLOWING PERORAL ADMINISTRATION OF CI-906 TO NORMAL HUMAN VOLUNTEERS AFTER ANGIOTENSIN-1 CHALLENGE. PROTOCOL 906-1"		
REVISED PAGE RR 724-00028 PG. 1 DATE: 22-JAN-85 PR. 906-1		

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DOC DATE	SER/SUPPL NO	TITLE
14-FEB-85	100	PR. 906-40
14-FEB-85	101	PR. 906-45
21-FEB-85	102	PR. 906-30
21-FEB-85	103	PR. 906-32
21-FEB-85	104	PR. 906-38
21-FEB-85	105	INFORMATION AMENDMENT
CONTENT: REVISED PAGES RR 745-00776 PGS. 49, 75, 76 AND 1282 DATE: 13-FEB-85 CROSS REFERENCE: SERIAL #10		
28-FEB-85	106	PR. 906-42
07-MAR-85	107	PR. 906-58 (MAD/104)
07-MAR-85	108	PR. 906-59 (MAD/105)
14-MAR-85	109	PR. 906-57 (PAR/34)
25-MAR-85	110	INFORMATION AMENDMENT
CONTENT: RR 724-00051 AUTHOR: GOULET, J.R. ET AL DATE: 21-MAR-85 "REPORT OF PROTOCOLS 906-6 AND -8: A 28-DAY DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL OF THE EFFICACY OF QUINAPRIL HYDROCHLORIDE (CI-906) IN THE TREATMENT OF MILD TO MODERATE HYPERTENSION; AND PROTOCOL 906-10, A LONG-TERM EXTENSION OF PROTOCOL 906-6"		
06-MAY-85	111	INFORMATION AMENDMENT
CONTENT: REVISED PAGES RR 764-00001 PGS. 1, 2/3, 6/7 AND 8/9 DATE: 10-APR-85 CROSS REFERENCE: SERIAL #1		

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20-MAY-85	112	NEW CO-INVESTIGATOR
CONTENT: PR. 906-17 SHEFFIELD, L. THOMAS		
28-JUN-85	113	IB UPDATE
CONTENT: DATE: 6-JUN-85 RR X-720-02145 AUTHOR: BUAKEMA, J. "INVESTIGATOR'S BROCHURE: CI-906" SUPERCEDES RR X-720-00952.		
16-JUL-85	114	NEW SUB-INVESTIGATOR
CONTENT: PR. 906-13 PAYNE, TOM, M.D.		
29-AUG-85	115	PR. 906-81
03-SEP-85	116	SAFETY REPORT
CONTENT: PATIENT NO.: 6 (MJM) PR. 906-30 RE: DEVELOPED HYPOTENSION. PROBABLY DRUG RELATED.		
16-SEP-85	117	SAFETY REPORT
CONTENT: PATIENT NO.: 11 PR. 906-61 (P.254) AE: DEATH NOT DRUG RELATED		
16-SEP-85	118	PR. 906-64
16-SEP-85	119	PR. 906-66
16-SEP-85	120	PR. 906-67
16-SEP-85	121	PR. 906-69

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16-SEP-85 122 PR. 906-72

23-SEP-85 123 LETTER RE: MANUFACTURING AND CONTROL  
CONTENT:

LETTER TO: DIVISION OF CARDIO-RENAL  
RR MEMO-963-01027  
RE: DATE ON OUR NEW 40 MG CONTROLLED RELEASE  
CAPSULES.

23-SEP-85 124 SAFETY REPORT  
CONTENT:

PATIENT NO.: 2 (GU)  
PR. 906-11 (P.215)  
AE: LIGHT-HEADEDNESS AND WOOZINESS IMMEDIATELY  
AFTER THE ADDITION OF CHLORTHALIDONE 25 MG  
TO QUINAPRIL 40 MG DAILY. SYMPTOMS RESOLVED  
ON DIURETIC WITHDRAWAL.  
DRUG RELATED.

PATIENT NO.: 22 (MH)  
PR. 906-11 (P.215)  
AE: BUSSING IN HEAD, HEAVINESS AND ACHING IN ARMS  
AND LEGS FROM THE DAY AFTER THE ADDITION OF  
CHLORTHALIDONE 25 MG TO QUINAPRIL 40 MG DAILY.  
SYMPTOMS RESOLVED ON DIURETIC WITHDRAWAL.  
DRUG RELATED.

23-SEP-85 124 SAFETY REPORT - CONTINUED  
CONTENT:

PATIENT NO.: 1 (DB)  
PR. 906-11 (P.215)  
AE: COMPLETE RIGHT HEMIPARESIS 5 DAYS AFTER THE  
ADDITION OF CHLORTHALIDONE 25 MG TO QUINAPRIL  
40 MG DAILY.  
DRUG RELATED.

PATIENT NO.: 10 (KW)  
PR. 906-11 (P.215)  
AE: NAUSEA, WEAKNESS, FATIGUE AND GENERALISED  
ACHES AND MUSCLE CRAMPS STARTING 3 DAYS AFTER  
MUSCLE CRAMPS STARTING 3 DAYS AFTER  
CHLORTHALIDONE 25 MG DAILY ADDED TO QUINAPRIL  
40 MG DAILY.  
DRUG RELATED.

PATIENT NO.: 24 (EB)  
PR. 906-11 (P.215)  
AE: MELAENA AND HB DROP FROM 14.9 TO 10.6 G/DL.  
DRUG RELATED

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DOC DATE	SER/SUPPL NO	TITLE
23-SEP-85	124	SAFETY REPORT - CONTINUED
CONTENT:		
PATIENT NO.: 31 (PC)		
PR. 906-11 (P.215)		
AE: DIZZINESS, PALPITATIONS, BREATHLESSNESS AND FEELING GENERALLY UNWELL ON THE FIFTH DAY AFTER DIURETIC ADDED.		
DRUG RELATED		
01-OCT-85	125	INFORMATION AMENDMENT
CONTENT:		
RR 745-00844		
AUTHOR: ANDERSON, J.A.		
DATE: 13-SEP-85		
"PERINATAL AND POSTNATAL STUDY IN RATS WITH CI-906"		
01-OCT-85	126	PROTOCOL AMENDMENT
CONTENT:		
AMENDMENT NO. 1		
PRS. 906-31, 32, 33, 34, 36, 37, 38, 40, 41, 43, 44, 45, 46		
DATE: 17-JUN-85		
PROVIDE ADDITIONAL BLOOD PRESSURE MEASUREMENTS.		
01-OCT-85	127	PROTOCOL AMENDMENT
CONTENT:		
AMENDMENT NO. 2		
PRS. 906-15, 16, 17, 18, 21 AND 22		
DATE: 10-JUN-85		
PROVIDES AND ADDITIONAL 12 MONTH CONTINUATION OF THE LONG-TERM, OPEN-LABEL PERIOD OF TREATMENT FOR PATIENTS RESPONDING TO QUINAPRIL HYDROCHLORIDE.		
01-OCT-85	128	PROTOCOL AMENDMENTS
CONTENT:		
AMENDMENTS NO. 4		
PR. 906-19		
DATE: 10-JUN-85		
PROVIDES AN ADDITIONAL 12 MONTH CONTINUATION OF THE LONG-TERM, OPEN-LABEL PERIOD OF TREATMENT FOR PATIENTS RESPONDING TO QUINAPRIL HYDROCHLORIDE.		
AMENDMENT NO. 5		
PR. 906-19		
DATE: NONE		
ALLOWS FOR 24 HOUR BLOOD PRESSURE MONITORING TO BE OBTAINED IN ALL PATIENTS IN THE OPEN-LABEL PERIOD WHO ARE RECEIVING CI-906 AS MONOTHERAPY FOR THEIR MILD TO MODERATE HYPERTENSION.		

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01-OCT-85 129 PROTOCOL AMENDMENTS  
CONTENT:

AMENDMENT NO. 3

PR. 906-15

DATE: NONE

ALLOWS 24 HOUR BLOOD PRESSURE MONITORING TO BE  
OBTAINED IN ALL PATIENTS IN THE OPEN-LABEL PERIOD  
WHO ARE RECEIVING CI-906 AS MONOTHERAPY FOR THEIR  
MILD TO MODERATE HYPERTENSION.

AMENDMENT NO. 2

PRS. 906-33, 44

DATE: NONE

ALLOW 24 HOUR BLOOD PRESSURE MONITORING TO BE  
OBTAINED IN ALL PATIENTS IN THE OPEN-LABEL PERIOD  
WHO ARE RECEIVING CI-906 AS MONOTHERAPY FOR THEIR  
MILD TO MODERATE HYPERTENSION.

14-OCT-85 130 SAFETY REPORT  
CONTENT:

PATIENT NO.: 21 (SSH)

PR. 906-11 (P.215)

AE: HYPERSENSITIVITY REACTION  
DRUG RELATED.

15-OCT-85 131 PR. 906-65

15-OCT-85 132 PR. 906-73

15-OCT-85 133 PR. 906-74

21-OCT-85 134 SAFETY REPORT  
CONTENT:

PATIENT NO.3

PR. 906-62 (UNITED KINGDOM)

NOT DRUG RELATED.

PATIENT NO. 6

PR. 906-62 (UNITED KINGDOM)

NOT DRUG RELATED.

PATIENT NO. 11

PR. 906-62 (UNITED KINGDOM)

NOT DRUG RELATED.

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DOC DATE	SER/SUPPL NO	TITLE
29-OCT-85	135	PR. 906-80 (MUN/664)
29-OCT-85	136	INFORMATION AMENDMENT
CONTENT: RR 740-01803 AUTHOR: FINK, G. ET AL DATE: 22-OCT-85/22/85 BY D. M. COHEN. "EFFECTS OF SEVERAL ACE INHIBITORS ON BRAIN CONVERTING ENZYME ACTIVITY IN NORMOTENSIVE RATS"		
29-OCT-85	137	INFORMATION AMENDMENT
CONTENT: REVISED PAGE RR X-720-02145 PG. 11 DATE: 25-SEP-85 CROSS REFERENCE: SERIAL #113		
29-OCT-85	138	PROTOCOL AMENDMENT
CONTENT: AMENDMENT NO. 2 PR. 906-12 DATE: 10-JUN-85 PROVIDES AN ADDITIONAL 12 MONTH CONTINUATION OF THE LONG-TERM, OPEN-LABEL PERIOD OF TREATMENT FOR PATIENTS RESPONDING TO QUINAPRIL HYDROCHLORIDE (CI-906).		
11-NOV-85	139	SAFETY REPORT
CONTENT: PATIENT NO.: 10 (LTT) PR. 906-34 AE: CARDIAC ARRHYTHMIA.		
21-NOV-85	140	PR. 906-99
27-NOV-85		LETTER RE: FDA REQUEST FOR INFORMATION
CONTENT: LETTER FROM: LIPICKY, RAYMOND J., M.D. RE: FDA REVIEWED INITIAL SUBMISSION WITH SEVERAL RECOMMENDATIONS AND REQUEST FOR INFORMATION.		
24-DEC-85	141	LETTER RE: REQUEST FOR INFORMATION
CONTENT: LETTER TO: LIPICKY, RAYMON J., M.D. RE: PROOF-OF-EFFICACY CLINICAL STUDIES: 1) TWO PROTOCOLS. 2) PRELIMINARY REPORT OF PHASE 2 MULTICENTER STUDIES. 3) REQUEST PERMISSION TO ADMINISTER THIS DRUG TO WOMEN OF CHILDBEARING POTENTIAL WHO ARE NOT PREGNANT OR NURSING AND ARE USING A RELIABLE METHOD OF CONTRACEPTION CONTROL		

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DOC DATE	SER/SUPPL NO	TITLE
30-DEC-85	142	SAFETY REPORT
CONTENT:		
PATIENT NO.: 24 (FLS)		
PR. 906-15		
AE: GASTROINTESTINAL BLEED		
08-JAN-86	143	SAFETY REPORT
CONTENT:		
PATIENT NO.: 17 (RL)		
PR. 906-36		
AE: DEVELOPED ATRIAL FIBRILLATION AND WAS		
HYPOKALEMIC.		
NOT DRUG RELATED.		
10-JAN-86	144	PR. 906-83
10-JAN-86	145	PR. 906-84
10-JAN-86	146	PR. 906-85
10-JAN-86	147	PR. 906-86
10-JAN-86	148	PR. 906-88
10-JAN-86	149	PR. 906-89
10-JAN-86	150	PR. 906-90
10-JAN-86	151	PR. 906-91
10-JAN-86	152	PR. 906-92
15-JAN-86	153	SAFETY REPORT
CONTENT:		
PATIENT NO.: 11 (NONE)		
PR. 906-17		
AE: CAROTID ENDARTERECTOMY FOLLOWING A SYCOPAL		
EPISODE.		
AE 001-0906-860002-00		



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DOC DATE	SER/SUPPL NO	TITLE
17-JAN-86	154	SAFETY REPORT
CONTENT: PATIENT NO.: 19 (OR) PR.: INTERNATIONAL STUDY AE: ACUTE MYOCARDIAL INFARCTION WHILE RECEIVING PLACEBO.		
24-JAN-86	155	LETTER RE: CONFIRMATION OF MEETING
CONTENT: LETTER TO: LIPICKY, RAYMOND J., M.D. RE: CONFIRMATION OF 12-FEB-86, 10 AM TO NOON MEETING IN ROCKVILLE, MARYLAND.		
30-JAN-86	156	ANNUAL REPORT
CONTENT: ISSUED DATE: 20-JAN-86		
31-JAN-86	157	PR. 906-82
31-JAN-86	158	PR. 906-63
31-JAN-86	159	PR. 906-68
31-JAN-86	160	PR. 906-75
31-JAN-86	161	PR. 906-76
10-FEB-86	162	PRS. 906-100, 102, 103, 104, 105, 106, 107, 108 (WLI 9-009-0)
17-FEB-86	163	SAFETY REPORT
CONTENT: PATIENT NO.: 3 (KAL) PR. 906-72 AE: CARDIA ARREST AND WAS RESUSCITATED. NOT DRUG RELATED. AE 001-0906-860003-00		
18-FEB-86	164	SAFETY REPORT
CONTENT: PATIENT NO.: 19 (NONE) PR. 906-30 AE: SUDDEN HEARING LOSS IN THE LEFT EAR. NOT DRUG RELATED. AE 001-0906-860004-00		

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18-FEB-86	165	PR. 906-87
03-MAR-86	166	SAFETY REPORT
CONTENT:		
PATIENT NO.: 13 (NONE)		
PR. 906-45		
AE: A TRANSIENT ARM NUMBNESS AND SPEECH DIFFICULTY.		
DRUG RELATED.		
AE 001-0906-860005-00		
04-MAR-86	167	MINUTES OF FDA MEETING
CONTENT:		
DATE: 12-FEB-86		
FDA MEETING CONCERNING THE QUINAPRIL HYDROCHLORIDE CLINICAL PROGRAM.		
06-MAR-86	168	SAFETY REPORT
CONTENT:		
PATIENT NO.: 3 (NONE)		
PR. 890-137		
AE: ICTERUS, CHOLOSTRASIS, DIAGNOSTIC MEASURES REVEALED PANCREATIC NEOPLASM AS CAUSE OF CHOLOSTRASIS.		
NOT DRUG RELATED.		
AE 049-0906-860001-00		
06-MAR-86	168	SAFETY REPORT - CONTINUED
CONTENT:		
PATIENT NO.: 6 (AF)		
PR. 044-0906-860004-01		
AE: TRANSIENT ISCHEMIC ATTACH (CEREBRAL)		
DRUG RELATED.		
AE 044-0906-860004-00		
06-MAR-86	168	SAFETY REPORT - CONTINUED
CONTENT:		
PATIENT NO.: 19 (WMY)		
PR. 9-003-4		
AE: TRANSIENT CEREBROVASCULAR ACCIDENT.		
AE 044-0906-860005-00		
06-MAR-86	169	LETTER RE: RESPONSE TO REQUEST FOR INFORMATION
CONTENT:		
LETTER TO: LIPICKY, RAYMOND J., M.D.		
RE: FDA'S 27-NOV-85 REQUEST FOR INFORMATION.		
1) RESPONSE BY MR. J.A. BOONSTRA CONCERNING THE ADDITIONAL MANUFACTURING AND CONTROLS DATA.		
2) RESPONSE BY MR. O.R. CANIS CONCERNING THE CONTAINER AND CLOSURE SYSTEM USED TO PACKAGE THE DRUG.		
3) REVISED PAGE X-720-02145		

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DOC DATE	SER/SUPPL NO	TITLE
14-MAR-86	170	SAFETY REPORT
CONTENT:		
PATIENT NO.: 19 (WDD)		
PR. 906-30		
AE: DEVELOPED A SUDDEN HEARING LOSS IN THE LEFT EAR.		
NOT DRUG RELATED.		
FOLLOW-UP REPORT - SERIAL #164		
24-MAR-86	171	SAFETY REPORT
CONTENT:		
PATIENT NO.: 13 (KEF)		
PR. 906-45		
AE: TRANSIENT ARM NUMBNESS AND SPEECH DIFFICULTY.		
DIAGNOSED AS NERVE PALSY.		
NOT DRUG RELATED.		
FOLLOW-UP REPORT - SERIAL #166		
AE 001-0906-860005-01		
24-MAR-86	172	SAFETY REPORT
CONTENT:		
PATIENT NO.: NONE (JH)		
PR. 906-48		
AE: CEREBRAL INSULT DURING THE OPEN LABEL PERIOD OF THE STUDY.		
AE 043-0906-860002-00		
24-MAR-86	172	SAFETY REPORT - CONTINUED
CONTENT:		
PATIENT NO.: 21 (JGM)		
SPAIN		
AE: URINARY RETENTION OF APPROXIMATELY 25 DAYS.		
AE 034-0906-860002-00		
25-MAR-86	173	SAFETY REPORT
CONTENT:		
PATIENT NO.: 10 (LTT)		
PR. 906-34		
AE: HAD A CARDIAC ARRHYTHMIA.		
SECONDARY TO HYPOKALEMIA.		
FOLLOW-UP - SERIAL #139		
27-MAR-86	174	PR. 906-60/INFORMATION AMENDMENT
CONTENT:		
RR MEMO-764-00505		
AUTHORS: FERRY, J.		
COLBURN, W.		
DATE: 17-FEB-86		
"CI-906: PROPOSED STUDY IN HUMAN SUBJECTS WITH		
14C-LABELED DRUG: ESTIMATION OF RADIATION IMPACT		
ON TARGET ORGANS"		

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27-MAR-86 175 ° INFORMATION AMENDMENT  
CONTENT:

RR 764-00441  
AUTHOR: TAYLOR, M. ET AL  
DATE: 13-FEB-86  
"CI-906 AND CI-928: A VALIDATED GAS  
CHROMATOGRAPHIC ASSAY FOR HUMAN PLASMA SAMPLES"

27-MAR-86 176 PRS. 906-114 TO 906-127, 131, 133, 134, 136

08-APR-86 177 SAFETY REPORT  
CONTENT:

PATIENT NO.: 3 (KAL)  
PR. 907-72  
AE: HAD A CARDIAC ARREST AND WAS RESUSCITATED.  
NOT DRUG RELATED.  
FOLLOW-UP REPORT - SERIAL #163  
AE 001-0906-860003-01

10-APR-86 178 PR. 906-93

10-APR-86 179 PRS. 906-128, 129, 130, 132

14-APR-86 180 LETTER RE: RESPONSE TO REQUEST FOR INFORMATION  
CONTENT:  
LETTER TO: LIPICKY, RAYMOND J., M.D.  
DATE: 11-APR-86  
RE: ADDITIONAL MANUFACTURING AND CONTROLS DATA AS  
REQUESTED IN FDA 27-NOV-85 LETTER.

14-APR-86 181 PR. 906-223

21-APR-86 182 PR. 906-95

21-APR-86 183 PR. 906-77

21-APR-86 184 PRS. 906-94 & 906-966

21-APR-86 185 SAFETY REPORT  
CONTENT:

PATIENT NO.: 16 (TCO)  
PR. 906-33  
AE: EXPERIENCED SHORTNESS OF BREATH WITH BRONCHIAL  
SPASM.  
DRUG RELATED.  
AE 001-0906-860006-00

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21-APR-86 185 SAFETY REPORT - CONTINUED  
CONTENT:

PATIENT NO.: 1 (WEP)  
PR. 906-86  
AE: EXPERIENCED CHEST PAIN AND SHORTNESS OF BREATH  
AND SYNCOPE.  
AE 001-0906-860007-00

23-APR-86 186 SAFETY REPORT  
CONTENT:

PATIENT NO.: 11 (JHO)  
PR. 906-91  
AE: DEVELOPED ARTHRALGIA, BACKACHE AND A LOW  
GRADE FEVER. MAY BE THE RESULT OF A VIRAL  
SYNDROME.  
AE 001-0906-860008-00

28-APR-86 187 PR. 906-91

28-APR-86 188 PR. 906-202

29-APR-86 189 LETTER RE: SUBMISSION CORRECTION  
CONTENT:

LETTER TO: CARDIO-RENAL DIVISION  
RE: INADVERTENTLY IDENTIFIED 28-APR-86, SERIAL  
NO. 188, IND AS 20,898.

01-MAY-86 190 SAFETY REPORT  
CONTENT:

PATIENT NO.: 1 (MA)  
PR. 85-791  
AE: DEVELOPED SYNCOPE.  
MAY BE DRUG RELATED.  
AE 049-9048-860001-00

01-MAY-86 190 SAFETY REPORT - CONTINUED  
CONTENT:

PATIENT NO.: 2 (NONE)  
PR. 9-009-0 - STUDY NO. 85-791  
AE: DEVELOPED FACIAL SRYTHEMA, CYANOSIS,  
ARTHRALGIA AND NAUSEA.  
DRUG RELATED.  
AE 032-906-860001-00

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02-MAY-86 191 SAFETY REPORT  
CONTENT:

PATIENT NO.: 1 (WEP)  
PR. 906-86  
AE: CHEST PAIN, SHORTNESS OF BREATH AND SYNCOPE.  
AE 001-0906-860007-01

05-MAY-86 192 PR. 906-209 (MUN/683)

05-MAY-86 193 PROTOCOL AMENDMENT  
CONTENT:

AMENDMENT NO. 1  
PRS. 906-63, 64, 65, 66, 67, 68, 69, 72, 73, 74  
75, 76, 77  
DATE: 7-MAR-86  
WOMEN OF CHILDBEARING POTENTIAL WHO ARE NOT  
PREGNANT OR BREAST FEEDING AND WHO USE A  
RELIABLE METHOD OF CONTRACEPTION FOR THE  
DURATION OF THE STUDY MAY PARTICIPATE.

07-MAY-86 194 SAFETY REPORT  
CONTENT:

PATIENT NO.: 24 (FLS)  
PR. 906-15  
AE: HOSPITALIZED WITH A GASTROINTESTINAL BLEEDING.  
DRUG RELATED.  
FOLLOW-UP REPORT - SERIAL #142

13-MAY-86 195 PRS. 906-137 & 138

13-MAY-86 196 PROTOCOL AMENDMENT  
CONTENT:

AMENDMENT NO. 1  
PRS. 906-114, 115, 116, 117, 118, 119, 120, 121,  
123, 124, 125, 126, 127, 128, 129, 130, 131,  
131, 133, 134 AND 136  
DATE: 1-MAR-86  
PROVIDES FOR HOURLY BLOOD PRESSURE AND HEART RATE  
MEASUREMENT AND RECORDING FOR PATIENTS.  
CROSS REFERENCE: SERIAL #176

13-MAY-86 197 PROTOCOL AMENDMENT  
CONTENT:

AMENDMENT NO. 1  
PR. 42  
DATE: 17-JUN-85  
PROVIDE FOR ADDITIONAL BLOOD PRESSURE MEASUREMENTS  
IN THE STUDY.  
CROSS REFERENCE: SERIAL #106

AMENDMENT NO. 1  
PRS. 906-20, 43  
DATE: 20-AUG-85

PROVIDE FOR TWICE A DAY DOSING OF QUINAPRIL  
HYDROCHLORIDE (CI-906) IN THE OPEN-LABEL PHASE  
OF PROTOCOL 906 CHLORTHALIDONE IN MILD TO  
MODERATE HYPERTENSIVE PATIENTS.  
CROSS REFERENCE: SERIAL #43

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DOC DATE	SER/SUPPL NO	TITLE
15-MAY-86		LETTER RE: CONFIRMATION OF AGREEMENT
CONTENT:		CROSSFILE IND 22,996, SERIAL NO. 179 LETTER TO: LIPICKY, RAYMOND J., M.D. RE: CONFIRMING THAT FDA HAS NO OBJECTIONS TO USING EITHER THE TREADMILL OR BICYCLE EROGMETER TEST IN EITHER/OR BOTH STUDIES (CI-914 AND/OR CI-906).
20-MAY-86	198	PROTOCOL AMENDMENTS
CONTENT:		AMENDMENT NO. 1 PRS. 82, 83, 84, 85, 86, 87, 88, 93, 94, 95 AND 96 DATE: 14-FEB-86 CHANGES THE DOSEAGE OF HYDROCHLOROTHIAZIDE TO 25 MG ONCE A DAY IN THE PLACEBO-BASELINE AND DOUBLE-BLIND PERIOD.  AMENDMENT NO. 2 PRS. 82, 83, 84, 85, 86, 88, 93, 94, 95 AND 96 DATE: 14-FEB-86 PROVIDE FOR THE PARTICIPATION OF WOMEN OF CHILD- BEARING POTENTIAL WHO ARE NOT PREGNANT OR BREAST FEEDING, AND WHO ARE ON A RELIABLE CONTRACEPTION FOR THE THE DURATION OF THEIR PARTICIPATION.
20-MAY-86	198	PROTOCOL AMENDMENTS - CONTINUED
CONTENT:		AMENDMENT NO. 3 PRS. 82, 83, 84, 85, 86, 94 AND 96 DATE: 28-APR-86 PROVIDES FOR THE EXCLUSION OF PATIENTS WITH ANTI-NUCLEAR ANTIGEN (ANA) TITERS OF GREATER THAN 1:40 AT THE TIME OF SCREENING, FROM ENTRY INTO THE PLACEBO BASELINE OR DOUBLE-BLIND PERIOD.
20-MAY-86	199	PROTOCOL AMENDMENT
CONTENT:		AMENDMENT NO.: 1 PRS. 906-11, CENTERS P.215, P.216, P.217, P.219, P.220 AND P.221 EXTENDS THE OPEN-LABELED PORTION OF THIS STUDY FOR A SECOND YEAR.
27-MAY-86	200	PR. 906-78



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DOC DATE	SER/SUPPL NO	TITLE
27-MAY-86	201	SAFETY REPORT
CONTENT:		
PATIENT NO.: 16 (HJ)		
PR. 906-48		
AE: DEATH		
NOT DRUG RELATED.		
AE 043-0906-860003-00		
29-MAY-86	202	SAFETY REPORT
CONTENT:		
PATIENT NO.: 6 (LWS)		
PR. 906-21		
AE: DEVELOPED HAIR LOSS.		
AE 001-0906-860009-00		
29-MAY-86	203	SAFETY REPORT
CONTENT:		
PATIENT NO.: 2 (MA)		
PR. 85-791		
AE: DEVELOPED PALPITATIONS, FLUSH, ARTHRALGIA AND NAUSEA.		
DRUG RELATED.		
AE 032-9016-860001-01		
05-JUN-86	204	SAFETY REPORT
CONTENT:		
PATIENT NO.: 10 (SMF)		
PR. 906-89		
AE: EXPERIENCED A SYNCOPE EPISODE.		
NOT DRUG RELATED.		
AE 001-0906-860010-00		
05-JUN-86	205	PROTOCOL AMENDMENT
CONTENT:		
AMENDMENT NO. 1		
PR. 906-78		
DATE: 7-MAR-86		
PROVIDES FOR THE PARTICIPATION OF WOMEN OF CHILDBEARING POTENTIAL WHO ARE NOT PREGNANT OR BREAST FEEDING, AND WHO ARE ON A RELIABLE CONTRACEPTIVE FOR THE DURATION OF THEIR PARTICIPATION IN THIS STUDY.		
10-JUN-86	206	SAFETY REPORT
CONTENT:		
PATIENT NO.: 7 (NONE)		
PR. 906-89		
AE: EXPERIENCED VIOLENT NAUSEA AND VOMITING 1-2 HOURS AFTER TAKING EACH DOSE OF MEDICATION.		
DRUG RELATED.		
AE 001-0906-860011-00		

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DOC DATE	SER/SUPPL NO	TITLE
10-JUN-86	207	INFORMATION AMENDMENT
CONTENT:		
RR 764-00523		
AUTHOR: FERRY, J. ET AL		
DATE: 16-MAY-86		
"CLINICAL BIOPHARMACEUTICAL STUDY OF TWO NEW		
PROTOTYPE FORMULATION CAPSULES OF QUINAPRIL		
(CI-906) AND AN IMMEDIATE-RELEASE CAPSULE.		
PROTOCOL 906-81"		
12-JUN-86	208	PR. 906-211
17-JUN-86	209	SAFETY REPORT
CONTENT:		
PATIENT NO.: 10 (HJ)		
PR. 906-48		
AE: DEATH DUE TO A CEREBRAL INSULT.		
NOT DRUG RELATED.		
AE 043-0906-860002-01		
17-JUN-86	209	SAFETY REPORT - CONTINUED
CONTENT:		
PATIENT NO.: 1 (K)		
PR. 890-211		
AE: INCREASE IN URIC ACID AND CREATININE LEVEL.		
17-JUN-86	209	SAFETY REPORT - CONTINUED
CONTENT:		
PATIENT NO.: 8 (NONE)		
PR. 891-157		
AE: SEVERE NAUSEA .		
17-JUN-86	209	SAFETY REPORT - CONTINUED
CONTENT:		
PATIENT NO.: NONE (TAR)		
PR. 9-003-4		
AE: DEATH - CEREBROVASCULAR ACCIDENT.		
NOT DRUG RELATED.		
17-JUN-86	209	SAFETY REPORT - CONTINUED
CONTENT:		
PATIENT NO.: 16 (HN)		
PR. 906-48		
AE: MYOCARDIAL INFARCTION.		
NOT DRUG RELATED.		

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CI NUMBER= 906 APPL NUMBER= 20,336

DOC DATE SER/SUPPL NO TITLE

17-JUN-86 210 INFORMATION AMENDMENT

CONTENT:

RR MEMO-764-00554

AUTHORS: FERRY, J.

COLBURN, W.

DATE: 30-APR-86

"PHARMACOKINETIC ASSESSMENT OF CI-928 FOLLOWING  
MULTIPLE DOSE ADMINISTRATION OF CI-906 TO PATIENT  
WITH MILD TO MODERATE HYPERTENSION. PROTOCOLS  
906: 12-22"

17-JUN-86 211 PR. 906-79

17-JUN-86 212 PR. 906-213 (WLI-9-015-0)

23-JUN-86 213 SAFETY REPORT

CONTENT:

PATIENT NO.: 3 (KAL)

PR. 906-72

AE: HAD A CARDIAC ARREST AND WAS RESUSCITATED.  
NOT DRUG RELATED.

AE 001-0906-860003-02

23-JUN-86 214 PROTOCOL AMENDMENTS

CONTENT:

AMENDMENT NO. 1

PR. 906-79

DATE: 7-MAR-86

PERMITS THE INCLUSION OF WOMEN OF CHILDBEARING  
POTENTIAL.

AMENDMENT NO. 2

PR. 906-79

DATE: 10-APR-86

ALLOWS PATIENTS TO ENROLL WITH FEV1 OF FVC OF AT  
LEAST 50% OF NORMAL.

23-JUN-86 215 PROTOCOL AMENDMENT

CONTENT:

AMENDMENT NO. 2

PRS. 906-63, 64, 65, 66, 67, 68, 69, 72, 73, 74,  
75, 76, 77 AND 78

DATE: 10-APR-86

ALLOWS ENROLLMENT OF PATIENTS WITH FEV1 OR FVC OF  
AT LEAST 50% OF NORMAL.

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02-JUL-86	216	SAFETY REPORT
CONTENT:		
PATIENT NO.: 6 (LWS)		
PR. 906-21		
AE: DEVELOPED HAIR LOSS.		
NOT DRUG RELATED.		
AE 001-0906-860009-01		
02-JUL-86	217	SAFETY REPORT
CONTENT:		
PATIENT NO.: 6 (CL)		
PR. 9-003-3		
AE: FLUID RETENTION AND OTHER SYMPTOMS.		
MAY BE DRUG RELATED.		
AE 033-0906-860003-02		
02-JUL-86	218	SAFETY REPORT
CONTENT:		
PATIENT NO.: 45 (CA)		
PR. 215-906-11		
AE: EXPERIENCED MUSCLE WEAKNESS, CRAMPS, POTASSIUM		
LOSS, ALKALOSIS AND IRON DEFICIENCY ANEMIA.		
NOT DRUG RELATED.		
AE 044-0906-860001-01		
02-JUL-86	219	PR. 906-144 (WLI 9-030-0)
02-JUL-86	220	PR. 906-188 (WLI 9-016-0)
10-JUL-86	221	PROTOCOL AMENDMENTS
CONTENT:		
AMENDMENT NO. 1		
PRS. 906-89, 90, 91, 92, 122, 137 AND 138		
DATE: 14-FEB-86		
CHANGES DOSAGE OF HYDROCHLOROTHIAZIDE TO 25 MG		
ONCE A DAY IN THE PLACEBO BASELINE AND THE		
DOUBLE-BLIND PERIOD.		
AMENDMENT NO. 2		
PRS. 87, 89, 90, 91, 92 AND 124		
DATE: 28-APR-86		
PROVIDES FOR THE EXCLUSION OF PATIENTS WITH		
ANTI-NUCLEAR ANTIGEN (ANA) TITERS OF GREATER		
THAN 1:40 AT THE TIME OF SCREENING.		
AMENDMENT NO. 3		
PRS. 88, 89, 90, 91, 92 AND 93		
DATE: 28-APR-86		
PROVIDES FOR THE EXCLUSION OF PATIENTS WITH ANTI-		
NUCLEAR ANTIGEN (ANA) TITERS OF GREATER THAN		
1:40 AT THE TIME OF SCREENING.		

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10-JUL-86	222	PR. 906-109 (WLI-9-009-0)
10-JUL-86	223	PR. 906-110 (WLI-9-009-0)
14-JUL-86	224	SAFETY REPORT
CONTENT:		
PATIENT NO.: 2 (KIN)		
PR. 906-66		
AE: DEATH FROM A PROBABLE ARRHYTHMIA.		
AE 001-0906-860012-00		
14-JUL-86	225	PROTOCOL AMENDMENTS
CONTENT:		
AMENDMENT NO. 1		
PR. 35		
DATE: 17-JUN-85		
PROVIDE FOR ADDITIONAL BLOOD PRESSURE MEASUREMENTS		
AMENDMENT NO. 2		
PRS. 906-31, 35, 36, 37, 38, 42, 45 AND 46		
DATE: 15-JUL-86		
PROVIDES FOR AN ADDITIONAL 12 MONTHS CONTINUATION		
OF THE LONG-TERM, OPEN LABEL PERIOD OF TREATMENT		
FOR PATIENTS RESPONDING TO QUINAPRIL		
HYDROCHLORIDE.		
AMENDMENT NO. 3		
PRS. 906-33, 35, 43, 44 AND 45		
DATE: 15-JUL-86		
PROVIDES FOR AN ADDITIONAL 12 MONTHS CONTINUATION		
OF THE LONG-TERM, OPEN LABEL PERIOD OF TREATMENT		
FOR PATIENTS RESPONDING TO QUINAPRIL		
HYDROCHLORIDE.		
14-JUL-86	225	PROTOCOL AMENDMENT - CONTINUED
CONTENT:		
AMENDMENT NO. 4		
PRS. 15 AND 44		
DATE: 1-NOV-84		
ALLOWS FOR THE USE OF CI-906 80.0 MG/DAY IN THE		
LONG-TERM PORTION OF THE DOSE RESPONSE STUDY FOR		
THOSE PATIENTS WHO HAVE NOT SHOWN THE DESIRED		
EFFICACY IN LOWERING BLOOD PRESSURE AT LOWER		
DOSES OF CI-906, AND WHO ARE ALSO FREE FROM ANY		
CLINICALLY SIGNIFICANT SIDE EFFECTS.		
21-JUL-86	226	PRS. 906-151, 152, 153, 154, 155, 163

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DOC DATE	SER/SUPPL NO	TITLE
21-JUL-86	227	INFORMATION AMENDMENT
CONTENT:		
RR 740-01706		
AUTHOR: UHLENDORF, P.D. ET AL		
DATE: 30-JUN-86		
"LIPID-REGULATING EFFECT OF CI-906, CI-907, AND CI-925 IN CHOLESTEROL-FED RATS: COMPARISON TO REFERENCE ACE INHIBITORS"		
RR 764-00556		
AUTHOR: FERRY, J. ET AL		
DATE: 11-JUN-86		
"EFFECT OF FOOD ON CI-906 (QUINAPRIL) AND CI-928 PHARMACOKINETICS FOLLOWING ORAL DOSING OF CI-906 TO HEALTHY SUBJECTS. PROTOCOL 906-80"		
28-JUL-86	228	SAFETY REPORT
CONTENT:		
PATIENT NO.: 5 (PHH)		
PR. 906-73		
AE: WORSENING OF CONGESTIVE HEART FAILURE AND DIABETES MELLITUS.		
AE 001-0906-860013-00		
04-AUG-86	229	PRS. 906-158, 159, 165 AND 200
04-AUG-86	230	SAFETY REPORT
CONTENT:		
PATIENT NO.: 10 (SC)		
PR. 906-85		
AE: DEVELOPED EXCESSIVE HYPOTENSION.		
AE 001-9016-860001-00		
04-AUG-86	230	SAFETY REPORT
CONTENT:		
PATIENT NO.: 19 (WMY)		
PR. 9-007-0		
AE: DEVELOPED A TRANSIENT CEREBRAL ISCHEMIC ATTACK.		
04-AUG-86	230	SAFETY REPORT
CONTENT:		
PATIENT NO.: 19 (WMY)		
PR. 9-003-4		
AE: EXPERIENCED A TRANSIENT CEREBROVASCULAR ACCIDENT WITH DISORIENTATION AND DECREASED RIGHT SIDED STRENGTH.		

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DOC DATE	SER/SUPPL NO	TITLE
15-AUG-86	231	PR. 906-156, 157 AND 192
15-AUG-86	232	PROTOCOL AMENDMENT
CONTENT:		
AMENDMENT NO. 3		
PRS. 906-63, 64, 65, 66, 67, 68, 69, 72, 73, 74, 75, 76, 77, 78		
DATE: 3-JUNE-86		
ALLOWS THE DELETION OF THE TREADMILL EXERCISE TEST (ETT) ON THE MORNING OF VISIT 3 (BEGINNING OF THE DOUBLE-BLIND PERIOD) FOR THOSE PATIENTS WHO HAVE COMPLETED TWO PREVIOUS VALID PLACEBO BASELINE ETTS.		
ALLOWS FOR THE SCHEDULING OF VISIT 3, 3 TO 7 DAY AFTER OBTAINING THE SECOND VALID PLACEBO BASELINE ETT.		
15-AUG-86	233	SAFETY REPORT
CONTENT:		
PATIENT NO.: NONE (MIC)		
PR. FRANCE		
AE: EXCESSIVE BLOOD PRESSURE RESPONSE AND HEPATITIS.		
AE 033-9048-860001-00		
15-AUG-86	233	SAFETY REPORT - CONTINUED
CONTENT:		
PATIENT NO.: NONE (MAG)		
PR. FRANCE		
AE: SYNCOPE AND ARTERIAL COLLAPSE.		
AE 033-0906-86004-00		
22-AUG-86	234	PRS. 906-141, 143, 145, 147, 149, 150, 161, 162, 166, 168, 169, 170, 195
28-AUG-86	235	PR. 906-160 (PAR/47)
28-AUG-86	236	PR. 906-199 (PAR/48)
28-AUG-86	237	PR. 906-183
02-SEP-86	238	SAFETY REPORT
CONTENT:		
PATIENT NO.: NONE ((MAG)		
PR. FRANCE		
AE: SYNCOPE AND ARTERIAL COLLAPSE		
AE 033-0906-860004-01		

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DOC DATE SER/SUPPL NO TITLE

02-SEP-86 239 SAFETY REPORT  
CONTENT:

PATIENT NO.: 6 (TES)  
PR. 906-127  
AE: TRANSIENT ISCHEMIC ATTACK.  
NOT DRUG RELATED  
AE 001-0906-860014-00

02-SEP-86 239 SAFETY REPORT - CONTINUED  
CONTENT:

PATIENT NO.: 6 (ESB)  
PR. 906-133  
AE: DEVELOPED SYNCOPE.  
AE 001-0906-860015-00

05-SEP-86 240 PR. 906-184

05-SEP-86 241 INFORMATION AMENDMENT  
CONTENT:

RR 764-00606  
AUTHOR: FERRY, J.J. ET AL  
DATE: 6-AUG-86  
"SINGLE DOSE TO ASSESS THE POTENTIAL DRUG-DRUG  
INTERACTION OF QUINAPRIL (CI-906) AND  
HYDROCHLOROTHIAZIDE (CI-570) IN BEAGLE DOGS"

18-SEP-86 242 PR. 906-186

18-SEP-86 243 INFORMATION AMENDMENT  
CONTENT:

RR MEMO-720-02260  
AUTHOR: PEARSE, S.B. ET AL  
DATE: 9-SEP-86  
"AN UPDATED INTERIM REPORT OF THE DOUBLE-BLIND  
PHASE OF A FIXED-DOSE, PLACEBO-CONTROLLED STUDY  
TO DETERMINE EFFICACY AND SAFETY OF ORALLY  
ADMINISTERED CI-906 IN PATIENTS WITH MILD TO  
MODERATE HYPERTENSION (PROTOCOL 906-11)"

29-SEP-86 244 SAFETY REPORT  
CONTENT:

PATIENT NO.: 4 (JJT)  
PR. 906-68  
AE: DEATH - PROBABLE MYOCARDIAL INFARCTION.  
NOT DRUG RELATED.  
AE 001-0906-860016-00



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DOC DATE	SER/SUPPL NO	TITLE
29-SEP-86	245	SAFETY REPORT
CONTENT:		
PATIENT NO.: 14 (ML)		
PR. 906-30		
AE: ELEVATED LIVER ENZYME LEVELS.		
NOT DRUG RELATED.		
AE 001-0906-860017-00		
03-OCT-86	246	PR. 906-187
03-OCT-86	247	PR. 906-185
03-OCT-86	248	PR. 906-229-0
10-OCT-86	249	PR. 906-182
13-OCT-86	250	SAFETY REPORT
CONTENT:		
PATIENT NO.: 16 (AEC)		
PR. 906-82		
AE: DEVELOPED ERTHEMA MULTIFORME.		
AE 001-0906-860002-00		
17-OCT-86	251	PR. 906-216
17-OCT-86	252	PR. 906-218
27-OCT-86	253	PRS. 906-172, 173, 174, 175, 176, 179
05-NOV-86	254	PRS. 906-171, 177, 180
05-NOV-86	255	PRS. 906-196, 197, 198
05-NOV-86	256	PR. 906-235-0
06-NOV-86	257	SAFETY REPORT
CONTENT:		
PATIENT NO.: 1 (FVR)		
PR. 906-133		
AE: ATRIAL FLUTTER.		
AE 001-0906-860018-00		

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DOC DATE	SER/SUPPL NO	TITLE
11-NOV-86	258	SAFETY REPORT
CONTENT:		
		PATIENT NO.: 5 (DES) PR. 906-120 AE: SEVERE ANGINA ATTACK. AE 001-0906-860019-00
14-NOV-86	259	PR. 906-204, 205 & 219/PROTOCOL AMENDMENT
CONTENT:		
		AMENDMENT NO. 1 PRS. 906-204, 205 AND 219 DATE: 7-MAR-86 PROVIDES FOR THE PARTICIPATION OF WOMEN OF CHILDBEARING POTENTIAL.
		AMENDMENT NO. 2 PRS. 906-204, 205 AND 206 DATE: 10-APR-86 ALLOW ENROLLEMENT OF PATIENTS WITH FEV1 OR FVC.
		AMENDMENT NO. 3 PRS. 906-204, 205 AND 206 DATE: 3-JUN-86 ALLOWS FOR THE DELETION OF THE TREADMILL EXERCISE TEST (ETT) ON THE MORNING OF VISIT 3 (BEGINNING OF THE DOUBLE-BLIND PERIOD)
14-NOV-86	260	PR. 906-226 CENTERS 1 AND 5
21-NOV-86	261	PR. 906-233 CENTERS 2 AND 4/PROTOCOL AMENDMENT
CONTENT:		
		AMENDMENT NO. 1 PRS. 906-311 CENTERS 2 AND 4 DATE: 7-MAR-86 PROVIDES FOR THE PARTICIPATION OF WOMEN OF CHILDBEARING POTENTIAL.
		AMENDMENT NO. 2 PRS. 906-311 CENTERS 2 AND 4 DATE: 10-APR-86 ALLOWS ENROLLMENT OF PATIENTS WITH FEV1 OR FVC.
		AMENDMENT NO. 3 PRS. 906-311 CENTERS 2 AND 4 DATE: 3-JUN-86 ALLOWS FOR THE DELETION OF THE TREADMILL EXERCISE TEST (ETT) ON THE MORNING OF VISIT 3 (BEGINNING OF THE DOUBLE-BLIND PERIOD).

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DOC DATE	SER/SUPPL NO	TITLE
21-NOV-86	262	PR. 906-226 CENTERS 8 AND 10
21-NOV-86	263	PRS. 906-226 CENTERS 11 & 12 - PRS. 906-277 CENTERS 11 & 12
02-DEC-86	264	PR. 906-234-0
02-DEC-86	265	PRS. 906-226 CENTERS 6 AND 7
02-DEC-86	266	INFORMATION AMENDMENT CONTENT: RR 740-02001 AUTHOR: KRAUSE, B. ET AL DATE: 14-NOV-86 "THE EFFECT OF QUINAPRIL ON PLASMA LIPID CONCENTRATION IN NORMAL RAT: COMPARISON OF REFERENCE ACE INHIBITORS"
09-DEC-86	267	PRS. 906-231 CENTERS 1, 2, 4, 6, 8, 9, 10 AND 11
16-DEC-86	268	ANNUAL REPORT CONTENT: ISSUED DATE: 16-DEC-86
16-DEC-86	269	PR. 906-231-5
16-DEC-86	270	PR. 906-230-0
16-DEC-86	271	INFORMATION AMENDMENT CONTENT: RR MEMO-720-02273 AUTHOR: PEARSE, S.B. ET AL DATE: 12-DEC-86 "AN INTERIM REPORT OF THE DOUBLE-BLIND PHASE OF A FIXED-DOSE, PLACEBO-CONTROLLED STUDY TO DETERMINE EFFICACY AND SAFETY OF ORALLY ADMINISTERED CI-906 IN PATIENTS WITH MILD TO MODERATE HYPERTENSION (PROTOCOL 906-11)"
16-DEC-86	272	INFORMATION AMENDMENT CONTENT: RR MEMO-724-00070 AUTHOR: FRANK, G. DATE: 8-DEC-86 "THE ACUTE HEMODYNAMIC EFFECTS OF QUINAPRIL, A NEW NON-SULFHYDRYL ANGIOTENSIN CONVERTING ENZYME INHIBITOR, IN PATIENTS WITH SEVERE CONGESTIVE CARDIAC FAILURE (PROTOCOL 906-61)"

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DOC DATE	SER/SUPPL NO	TITLE
16-DEC-86	273	INFORMATION AMENDMENT
CONTENT:		
RR 764-00652		
AUTHOR: FERRY, J.J. ET AL		
DATE: 12-NOV-86		
"BIOAVAILABILITY AND PHARMACOKINETICS OF QUINAPRIL (CI-906) AND ITS ACTIVE METABOLITE (CI-928) FOLLOWING SINGLE ORAL AND INTRAVENOUS QUINAPRIL AND CI-928 DOSES ADMINISTERED TO BEAGLE DOGS"		
22-DEC-86	274	SAFETY REPORT
CONTENT:		
PATIENT NO.: 9 (JG)		
PR. 906-120		
AE: DEVELOPED FACIAL SWELLING, RASH, DIZZINESS AND HEADACHES.		
NOT DRUG RELATED.		
AE 001-9999-8600004-00		
30-DEC-86	275	PR. 906-231 CENTERS 3, 7 AND 12
06-JAN-87	276	PR. 906-226 CENTERS 2 AND 4
06-JAN-87	277	PR. 906-227-2
13-JAN-87	278	PR. 906-226-3
13-JAN-87	279	PR. 906-227-3
23-JAN-87	280	PR. 906-226-13
23-JAN-87	281	PR. 906-227-13
23-JAN-87	282	IB UPDATE
CONTENT:		
DATE: 12-DEC-86		
RR X-720-02277		
AUTHOR: FRANK, G. ET AL		
"INVESTIGATOR'S BROCHURE: QUINAPRIL HYDROCHLORIDE (CI-906)"		

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DOC DATE	SER/SUPPL NO	TITLE
30-JAN-87	283	PROTOCOL ADDENDUM
CONTENT:		
ADDENDUM NO.: NONE		
PR. 906-266		
DATE: 19-JAN-87		
REPLACE THE CAPSULE WITH THE TABLET FORMULATION.		
10-FEB-87	284	SAFETY REPORT
CONTENT:		
PATIENT NO.: 2 (DJ)		
PR. 906-72		
AE: DEATH - PNEUMONIA AND SEPTIC SHOCK.		
DRUG RELATED.		
AE 001-0906-870001-00		
10-FEB-87	285	PR. 906-239-0
10-FEB-87	286	INFORMATION AMENDMENT
CONTENT:		
RR MEMO-710-00354		
AUTHOR: ELLIS, J.E. ET AL		
DATE: 14-JAN-87		
"CI-906, BULK DRUG SUBSTANCE: REVISED		
MANUFACTURING AND ANALYTICAL SPECIFICATIONS FOR		
IND FILING"		
17-FEB-87	287	PROTOCOL ADDENDUM
CONTENT:		
ADDENDUM NO.: NONE		
PR. 906-226		
REVISED PAGES 6 (SECTION B5), 7 (SECTION C9),		
16 (SECTION E), 8 (SECTION D), 7 (SECTION C2),		
7 (SECTION C5), 12 (SECTION 3.6), 13 (SECTION		
2.4), 14 (SECTION 3), 14 (SECTION 4.6), 15		
(SECTION 5(C)), 9 (SECTION V.A1), 15 (SECTION 6		
(B)), 19 (SECTION B2), 5, 11, 16 (SECTION VI,A),		
17 (B), 17 (B1), 17 (B3), 17 (B2) AND 6 (SECTION		
IV,A)		
INCLUDED A REVISED COPY OF THE PROTOCOL WITH		
THE ABOVE MENTIONED REVISIONS.		
17-FEB-87	288	PR. 906-226-9
17-FEB-87	289	PR. 906-227 CENTERS 8, 9 AND 10

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DOC DATE	SER/SUPPL NO	TITLE
24-FEB-87	290	PR. 906-226-14
24-FEB-87	291	PR. 906-227 CENTERS 4 AND 14
24-FEB-87	292	PR. 906-249-0
04-MAR-87	293	LETTER RE: MANUFACTURING AND CONTROLS
CONTENT: LETTER TO: DIVISION OF CARDIO-RENAL RR X-969-00022 RE: UPDATED DATA FOR 0.0625, 1.0, 1.25, 2.5, 5, 10, 20 AND 40 MG CAPSULES; 40 MG CONTROLLED RELEASE CAPSULES; AND 1.25, 2.5, 5, 10, 20 AND 40 MG TABLETS.		
04-MAR-87	294	SAFETY REPORT
CONTENT: PATIENT NO.: 1 (WES) PR. 906-75 AE: DEATH AE 001-0906-870002-00		
04-MAR-87	295	PROTOCOL AMENDMENT
CONTENT: AMENDMENT NO. 3 PR. 906-79 DATE: 3-JUN-86 ALLOWS FOR THE DELETION OF THE TREADMILL EXERCISE TEST (ETT) ON THE MORNING OF VIST 3 (BEGINNING OF THE DOUBLE-BLIND PERIOD).		
04-MAR-87	296	INFORMATION AMENDMENT
CONTENT: RR 764-00663 AUTHOR: FERRY, J.J. ET AL DATE: 5-JAN-87 "EFFECT OF CIMETIDINE ON SINGLE DOSE PHARMACOKINETICS OF QUINAPRIL AND ITS ACTIVE METABOLITE (CI-928) IN HEALTHY VOLUNTEERS: PROTOCOL 906-113"		
09-MAR-87	297	SAFETY REPORT
CONTENT: PATIENT NO.: 4 (KIN) PR. 906-66 AE: DEATH - ARRHYTHMIA PATIENT'S NO. WAS INADVERTENTLY SUBMITTED AS 2. FOLLOW-UP REPORT - SERIAL #297 AE 001-0906-860012-01		

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DOC DATE	SER/SUPPL NO	TITLE
09-MAR-87	298	PR. 906-237-0
09-MAR-87	299	INFORMATION AMENDMENT
CONTENT:		
RR: 764-00635		
AUTHOR: FERRY, J.J. ET AL		
DATE: 14-JAN-87		
"CLINICAL BIOEQUIVALENCE STUDY COMPARING THREE QUINAPRIL CAPSULES AND A QUINAPRIL ORAL SOLUTION. PROTOCOL 906-99"		
11-MAR-87	300	SAFETY REPORT
CONTENT:		
PATIENT NO.: 23 (AWT)		
PR. 906-46		
AE: DEVELOPED ANEMIA.		
NOT DRUG RELATED.		
AE 001-0906-870003-00		
11-MAR-87	301	INFORMATION AMENDMENT
CONTENT:		
REVISED PAGE FOR PRL. 906-249-0		
PG. 3		
PAGE WAS MISSING WHEN THE PROTOCOL WAS ORGINALLY FILED.		
12-MAR-87	302	SAFETY REPORT
CONTENT:		
PATIENT NO.: 1 (WES)		
PR. 906-75		
AE: DEATH		
NOT DRUG RELATED.		
FOLLOW-UP REPORT - SERIAL #294		
AE 001-0906-870002-01		
12-MAR-87	303	SAFETY REPORT
CONTENT:		
PATIENT NO.: 9 (RGB)		
PR. 906-122		
AE: DEATH		
AE 001-0906-870004-00		
12-MAR-87	304	SAFETY REPORT
CONTENT:		
PATIENT NO.: 13 (KES)		
PR. 906-45		
AE: EXPERIENCED A MYOCARDIAL INFARCTION.		
AE 001-0906-870005-00		

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DOC DATE	SER/SUPPL NO	TITLE
12-MAR-87	305	PROTOCOL AMENDMENT
CONTENT: AMENDMENT NO. 1 PR. 906-230-0 CHANGES THE TREATMENT FROM A SINGLE 40 MG CAPSULE TO TWO 20 MG CAPSULES.		
12-MAR-87	306	INFORMATION AMENDMENT
CONTENT: RR 764-00740 AUTHOR: FERRY, J.J. ET AL DATE: 17-FEB-87 "CLINICAL BIOAVAILABILITY STUDY COMPARING TWO PROTOTYPE QUINAPRIL TABLET FORMULATIONS, A QUINAPRIL CAPSULE FORMULATION, AND A QUINAPRIL ORAL SOLUTION, PROTOCOL 906-202"		
16-MAR-87	307	SAFETY REPORT
CONTENT: PATIENT NO.: 5 (JAB) PR. 906-96 AE: HAD CORNARY ARTERY BYPASS SURGERY. NOT DRUG RELATED. AE 001-0906-870006-00		
16-MAR-87	308	SAFETY REPORT
CONTENT: PATIENT NO.: 6 (DK) PR. 906-138 AE: HAD A MASTECTOMY. NOT DRUG RELATED. AE 001-0906-870007-00		
16-MAR-87	309	SAFETY REPORT
CONTENT: PATIENT NO.: 8 (TJK) PR. 906-77 AE: EXPERIENCED A COMPLETE HEART BLOCK. AE 001-0906-870008-00		
16-MAR-87	310	PR. 906-226 CENTERS 17 AND 18
16-MAR-87	311	PR. 906-226-18



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DOC DATE	SER/SUPPL NO	TITLE
19-MAR-87	312	SAFETY REPORT
CONTENT: PATIENT NO.: 24 (WKH) PR. 906-33 AE: LOSS OF CONSCIOUSNESS. AE 001-0906-870009-00		
19-MAR-87	313	PR. 906-242-07
19-MAR-87	314	INFORMATION AMENDMENT
CONTENT: RR X-720-02147 AUTHOR: FRANK, G.J. ET AL DATE: 12-FEB-87 "OVERALL REPORT OF A MULTICENTER, FIXED-DOSE, DOUBLE-BLIND, PLACEBO-CONTROLLED, SIX-WEEK STUDY OF THE EFFICACY AND SAFETY OF ORALLY ADMINISTERED QUINAPRIL HYDROCHLORIDE (CI-906) IN PATIENTS WITH MILD TO MODERATE HYPERTENSION"		
26-MAR-87	315	PR. 906-183X
26-MAR-87	316	PR. 906-226-19
26-MAR-87	317	PR. 906-227-19
26-MAR-87	318	PRS. 906-228 CENTERS 1,2,3,4,5,7,8,9,10,13,14,18,19,20,22,24
26-MAR-87	319	SAFETY REPORT
CONTENT: PATIENT NO.: 1 PR. 906-218 AE: AN ACUTE MYOCARDIAL INFARCTION. NOT DRUG RELATED. AE 001-9999-8700001-00		
31-MAR-87	320	SAFETY REPORT
CONTENT: PATIENT NO.: 8 (TJK) PR. 906-77 AE: EXPERIENCED A COMPLETE HEART BLOCK. NOT DRUG RELATED. FOLLOW-UP REPORT - SERIAL #309 AE 001-0906-870008-01		

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DOC DATE	SER/SUPPL NO	TITLE
02-APR-87	321	PRS. 906-238 CENTERS 12, 15, 16, 21, 25, 26
02-APR-87	322	PRS. 906-226 CENTERS 20 AND 21
02-APR-87	323	PR. 906-227-20
02-APR-87	324	SAFETY REPORT
CONTENT:		
PATIENT NO.: 60		
PR. WLI 9-003-0		
AE: MYOCARDIAL INFARCTION 11 DAY AFTER STARTING		
ENALPRIL THERAPY.		
NOT DRUG RELATED.		
AE 033-9048-860002-00		
02-APR-87	324	SAFETY REPORT - CONTINUED
CONTENT:		
PATIENT NO.: 361 (NONE)		
PR. WLI 9-003-4		
AE: BLEEDING TENDENCY.		
DRUG RELATED.		
AE 060-0906-860001-00		
02-APR-87	324	SAFETY REPORT - CONTINUED
CONTENT:		
PATIENT NO.: 45 (NONE)		
PR. WLI 9-030-0		
AE: SUSPECTED MYOCARDIAL INFARCTION.		
NOT DRUG RELATED.		
AE 044-0906-860001-01		
02-APR-87	324	SAFETY REPORT - CONTINUED
CONTENT:		
PATIENT NO.: 24 (NONE)		
PR. 906-11		
AE: CHEST PAIN.		
NOT DRUG RELATED.		
AE 358-0906-87000-00		
03-APR-87	325	SAFETY REPORT
CONTENT:		
PATIENT NO.: 1 (NONE)		
PR. WLI 9-008-1		
AE: PATIENT HAD AN ERYTHEMATOUS ERUPTION AND		
PRURITUS WHICH DEVELOPED WHILE PARTICIPATING		
IN THE STUDY.		
POSSIBLE DRUG RELATED.		
AE 033-0906-860005-00		

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DOC DATE	SER/SUPPL NO	TITLE
06-APR-87	326	SAFETY REPORT
CONTENT:		
PATIENT NO.: 2 (DJ)		
PR. 906-72		
AE: DEATH - PNEUMONIA AND SEPTIC SHOCK.		
NOT DRUG RELATED		
FOLLOW-UP REPORT - SERIAL #248		
AE 033-0906-860005-00		
06-APR-87	327	PR. 906-238-23
14-APR-87	328	SAFETY REPORT
CONTENT:		
PATIENT NO.: 23 (AWT)		
PR. 906-46		
AE: DEVELOPED ANEMIA.		
NOT DRUG RELATED.		
FOLLOW-UP REPORT - SERIAL #300		
AE 001-0906-870003-01		
14-APR-87	329	PR. 906-238 CENTERS 11 AND 27
22-APR-87	330	PRS. 906-226-15, 16, 32, 34/ 906-238-22 THRU 30, 32
22-APR-87	331	PR. 906-227 CENTERS 22, 24, 25, 26, 28, 29, 32, 33, 34
22-APR-87	332	SAFETY REPORT
CONTENT:		
PATIENT NO.: 4 (JJT)		
PR. 906-68		
AE: DEATH - MYOCARDIAL INFARCTION.		
AE 001-0906-860016-01		
24-APR-87	333	SAFETY REPORT
CONTENT:		
PATIENT NO.: 3 (RAC)		
PR. 906-35		
AE: HAD AN ACUTE MYOCARDIAL INFARCTION.		
AE 001-0906-870010-00		
24-APR-87	334	PR. 906-244-0

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24-APR-87 335 PR. 906-233-5

01-MAY-87 336 SAFETY REPORT  
CONTENT:

PATIENT NO.: 8 (TJK)  
PR. 906-77  
AE: EXPERIENCED A COMPLETE HEART BLOCK.  
NOT DRUG RELATED.  
FOLLOW-UP REPORT - SERIAL #309  
AE 001-0906-870008-02

01-MAY-87 337 SAFETY REPORT  
CONTENT:

PATIENT NO.: 345 (BMA)  
PR. 9-003-4  
AE: DEATH  
POSSIBLY DRUG RELATED.  
AE 032-0906-870001-00

04-MAY-87 338 PROTOCOL AMENDMENT  
CONTENT:

AMENDMENT NO. 4  
PRS. 906-63, 64, 65, 66, 67, 68, 69, 72, 73, 75,  
77, 78, 79, 204, 205, 216, 218, 219 & 233-2  
DATE: 29-DEC-86  
PERMITS WEEKLY CLINICAL VISITS TO BE OPTIONAL AT  
THE INVESTIGATOR'S DISCRETION FOR PATIENTS WHO  
ARE STABLE.  
DRUG ASSAY WILL BE REQUIRED AT SPECIFIC DOUBLE-  
BLIND VISITS.

12-MAY-87 339 SAFETY REPORT  
CONTENT:

PATIENT NO.: 5 (BW)  
PR. 906-67  
AE: EXPERIENCED SWELLING OF THE TONGUE.  
AE 001-0906-870012-00

12-MAY-87 340 SAFETY REPORT  
CONTENT:

PATIENT NO.: 1 (CFO)  
PR. 906-219  
AE: DEATH  
NOT DRUG RELATED.  
AE 001-0906-870011-00

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12-MAY-87 341 PROTOCOL AMENDMENT  
CONTENT:

AMENDMENT NO. 4  
PR. 906-94  
DATE: AUG-86  
PROVIDES FOR EVALUATION OF QUINAPRIL THERAPY ON  
PLASMA LIPIDS AND MONITORS THE EFFICACY OF  
QUINAPRIL IN LOW AND NORMAL-RENIN SUBGROUPS.

AMENDMENT NO. 5  
PR. 906-94  
DATE: 4-MAR-87  
PROVIDES FOR HOURLY BLOOD PRESSURE MONITORING.

12-MAY-87 342 PROTOCOL AMENDMENT  
CONTENT:

AMENDMENT NO. 3  
PR. 906-22  
PROVIDES FOR AN ADDITIONAL 12 MONTH CONTINUATION  
OF OPEN-LABEL TREATMENT.

19-MAY-87 343 PR. 906-254-0

19-MAY-87 344 PROTOCOL AMENDMENT  
CONTENT:

AMENDMENT NO. 5  
PRS. 906-63, 64, 65, 66, 67, 68, 69, 72, 73, 75,  
77, 78, 79, 204, 205, 216, 218, 219, AND  
233-2  
DATE: 13-FEB-87  
ADDS AN EXCLUSION FOR PATIENTS BASED ON ANA TITER.

19-MAY-87 345 PR. 906-226-35

19-MAY-87 346 PR. 906-227-35

19-MAY-87 347 PR. 906-246 CENTERS 1, 3, 4 AND 5

26-MAY-87 348 SAFETY REPORT  
CONTENT:

PATIENT NO.: 16 (SOP)  
PR. 906-68  
AE: DEATH  
NOT DRUG RELATED.  
AE 001-0906-870013-00

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DOC DATE	SER/SUPPL NO	TITLE
26-MAY-87	349	PR. 906-252 CENTERS 1 AND 2
26-MAY-87	350	PROTOCOL AMENDMENT
CONTENT:		
AMENDMENT NO. 1		
PR. 906-231-1		
DATE: 10-FEB-87		
ESTABLISHES A MAXIMUM ALLOWABLE RISE IN CREATININE TO A VALUE OF 2.5 MG/DL.		
26-MAY-87	351	INFORMATION AMENDMENT
CONTENT:		
RR 764-00771		
AUTHOR: HORVATH, A.M. ET AL		
DATE: 13-APR-87		
"CLINICAL BIOAVAILABILITY STUDY COMPARING TWO PROTOTYPE QUINAPRIL TABLET FORMULATIONS AND A QUINAPRIL CAPSULE FORMULATION, PROTOCOL 906-234"		
26-MAY-87	352	INFORMATION AMENDMENT
CONTENT:		
RR 720-02331		
AUTHOR: IMBARRATO, C. ET AL		
DATE: 15-MAY-87		
"EFFECTS OF ORAL QUINAPRIL ON BLOOD PRESSURE, HEART RATE, AND PULMONARY FUNCTION MEASUREMENTS IN HEALTHY SUBJECTS (PROTOCOL 906-232-0)"		
26-MAY-87	353	INFORMATION AMENDMENT
CONTENT:		
RR X-720-02185		
AUTHOR: FRANK, G.J. ET AL		
DATE: 8-MAY-87		
"OVERALL REPORT OF A MULTICENTER, DOUBLE-BLIND, PLACEBO-CONTROLLED, 12-WEEK STUDY COMPARING THE EFFICACY AND SAFETY OF ONCE-A-DAY, ORALLY-ADMINISTERED QUINAPRIL HYDROCHLORIDE (CI-906) WITH CHLORTHALIDONE AND WITH CONCOMITANT QUINAPRIL PLUS CHLORTHALIDONE IN PATIENTS WITH MILD TO MODERATE HYPERTENSION"		
27-MAY-87	354	SAFETY REPORT
CONTENT:		
PATIENT NO.: 2 (SJ)		
PR. 891-151		
AE: DEATH - CARDIOMYOPATHY SECONDARY TO CHF.		
AE 049-0906-870005-00		

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DOC DATE	SER/SUPPL NO	TITLE
02-JUN-87	355	PR. 906-246-2
02-JUN-87	356	PR. 906-247 CENTERS 2, 3, 4
02-JUN-87	357	PRS. 906-250 CENTERS. 1 AND 2
02-JUN-87	358	INFORMATION AMENDMENT
CONTENT:		
RR 764-00786		
AUTHOR: MCNALLY, W. ET AL		
DATE: 27-APR-87		
"WHOLE-BODY AUTORADIOGRAPHIC ANALYSIS OF TISSUE DISTRIBUTION OF 14-C-CI-906 IN RATS"		
02-JUN-87	359	INFORMATION AMENDMENT
CONTENT:		
RR 764-00779		
AUTHOR: FERRY, J.J. ET AL		
DATE: 24-APR-87		
"SINGLE DOSE PHARMACOKINETIC DRUG-DRUG INTERACTION STUDY OF QUINAPRIL (CI-906) AND HYDROCHLOROTHIAZIDE (CI-570) IN HEALTHY VOLUNTEERS. PROTOCOL 906-221"		
02-JUN-87	360	PR. 906-226-31
09-JUN-87	361	PR. 906-251-1
09-JUN-87	362	INFORMATION AMENDMENT
CONTENT:		
RR MEMO-720-02325		
AUTHOR: FRANK, G.J. ET AL		
DATE: 22-MAY-87		
"TWENTY-FOUR BLOOD PRESSURE AND HEART RATE RESPONSES TO ONCE-DAILY QUINAPRIL HYDROCHLORIDE (CI-906) MEASURED BY AMBULATORY MONITORING IN HYPERTENSIVE PATIENTS RECEIVING OPEN-LABEL QUINAPRIL (PROTOCOLS 906-33 AND 906-25)"		
16-JUN-87	363	PR. 906-251-2
16-JUN-87	364	PR. 906-253-1

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DOC DATE	SER/SUPPL NO	TITLE
16-JUN-87	365	PR. 906-258-1
18-JUN-87	366	PR. 906-259-0
25-JUN-87	367	PR. 906-250-3
25-JUN-87	368	INFORMATION AMENDMENT
CONTENT: RR 764-007092 AUTHOR: FERRY, J.J. ET AL DATE: 8-JUN-87 "EFFECT OF QUINAPRIL ON THE MULTIPLE DOSE PHARMACOKINETICS OF DIGOXIN IN HEALTHY VOLUNTEERS, PROTOCOL 906-209"		
29-JUN-87	369	SAFETY REPORT
CONTENT: PATIENT NO.: 5 (BW) PR. 906-67 AE: EXPERIENCED SWELLING OF THE TONGUE. POSSIBLY DRUG RELATED. AE 001-0906-870012-01		
07-JUL-87	370	PR. 906-256-0
07-JUL-87	371	PROTOCOL AMENDMENTS
CONTENT: AMENDMENT NO. 2 PRS. 906-114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 125, 126, 127, 128, 129, 131, 132, 133, 134, 136, 137 AND 138 DATE: 25-AUG-86 ALLOWS PEAK (POST DOSE) MONITORING FOR BLOOD PRESSURE AND HEART RATE MEASUREMENTS TO BE OPTIONAL FOR PATIENTS NOT REQUIRING TITRATION OR ADDITION OF HYDROCHLOROTHIAZIDE.  AMENDMENT NO. 3 PRS. 906-124 DATE: 25-AUG-86 ALLOWS PEAK (POST DOSE) MONITORING FOR BLOOD PRESSURE AND HEART RATE MEASUREMENTS TO BE OPTIONAL FOR PATIENT NOT REQUIRING TITRATION OR ADDITION OF HYDROCHLOROTHIAZIDE.		



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22-JUL-87	372	INFORMATION AMENDMENT
CONTENT:		
REVISED PAGE RR X-720-02277		
PG. 5		
DATE: 15-JUL-87		
CROSS REFERENCE: SERIAL #17		
22-JUL-87	373	LETTER RE: PROTOCOL CANCELLATION
CONTENT:		
PR. 906-152		
RE: CANCELLATION OF PROTOCOL		
22-JUL-87	374	PROTOCOL AMENDMENTS
CONTENT:		
AMENDMENT NO. 1		
PR. 906-30		
DATE: 17-JUN-85		
PROVIDE FOR ADDITIONAL BLOOD PRESSURE MEASUREMENTS		
AMENDMENT NO. 2		
PRS. 906-30, 32, 41 AND 130		
DATE: 20-AUG-85		
PROVIDES FOR TWICE A DAY DOSING OF QUINAPRIL HCL (CI-906) IN THE OPEN-LABEL PHASE OF PROTOCOL 906, CHLORTHALIDONE IN MILD TO MODERATE HYPERTENSIVE PATIENTS.		
AMENDMENT NO. 3		
PRS. 906-30, 31, 34, 36, 37, 38 AND 41		
DATE: 31-AUG-86		
PROVIDES FOR AN ADDITIONAL 12 MONTH CONTINUATION OF THE LONG-TERM, OPEN LABEL PERIOD OF TREATMENT.		
22-JUL-87	374	PROTOCOL AMENDMENTS - CONTINUED
CONTENT:		
AMENDMENT NO. 4		
PR. 906-33		
DATE: 20-AUG-85		
PROVIDES FOR TWICE A DAY DOSING OF QUINAPRIL HYDROCHLORIDE (CI-906) IN THE OPEN-LABEL PHASE OF PROTOCOL 906, CHLOROTHALIDONE IN MILD TO MODERATE HYPERTENSIVE PATIENTS.		
22-JUL-87	375	PROTOCOL AMENDMENT
CONTENT:		
AMENDMENT NO. 1		
PR. 906-250-1		
DATE: NONE		
PROVIDES FOR ADDITIONAL BLOOD PRESSURE MEASUREMENT AND A CLINICAL LABORATORY, ELECTROCARDIOGRAM, AND PHYSICAL EXAMINATION.		

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22-JUL-87	376	INFORMATION AMENDMENT
CONTENT:		
		RR 250-01471 AUTHOR: ROGERS, S.C. ET AL DATE: 8-JUL-87 "ACUTE ORAL TOXICITY STUDY OF CI-955 (QUINAPRIL- HYDROCHLOROTHIAZIDE COMBINATION) IN MICE"
		RR 250-01484 AUTHOR: ROGERS, S.C. ET AL DATE: 8-JUL-87 "ACUTE ORAL TOXICITY STUDY OF CI-955 (QUINAPRIL- HYDROCHLOROTHIAZIDE COMBINATION) IN RATS"
22-JUL-87	377	INFORMATION AMENDMENT
CONTENT:		
		RR 764-00808 AUTHOR: FERRY, J.J. ET AL DATE: 26-JUN-87 "SINGLE-DOSE, BIOEQUIVALENCE STUDY COMPARING QUINAPRIL 2.5-MG MARKET-IMAGE TABLETS AND QUINAPRIL 20-MG CAPSULES IN HEALTHY VOLUNTEERS, PROTOCOL 906-239"
		RR 764-00820 AUTHOR: HORVATH, A.M. ET AL DATE: 26-JUN-87 "EFFECT OF MULTIPLE-DOSE PROPRANOLOL ADMINISTRATION ON SINGLE-DOSE PHARMACOKINETICS OF QUINAPRIL AND ITS ACTIVE METABOLITE (CI-928) IN HEALTHY VOLUNTEERS. PROTOCOL 906-229"
22-JUL-87	378	INFORMATION AMENDMENT
CONTENT:		
		RR MEMO-720-02335 AUTHOR: FRANK, G.J. ET AL DATE: 1-JUN-87 "GLOBAL RESPONSE ADDENDUM TO QUINAPRIL (CI-906) FIXED-DOSE MULTICENTER STUDY (RR-X-720-02147)"
31-JUL-87	379	LETTER RE: REQUEST FOR MEETING
CONTENT:		
		LETTER TO: LIPICKY, J., M.D. RE: REQUESTING A MEETING CONCERNING DEVELOPMENT OF A COMBINATION DRUG PRODUCT CONSISTING OF QUINAPRIL AND HYDROCHLOROTHIAZIDE.

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DOC DATE	SER/SUPPL NO	TITLE
31-JUL-87	380	PR. 906-255-0
31-JUL-87	381	INFORMATION AMENDMENT
CONTENT:		
RR 724-00072 AUTHOR: FRANK, G.J. ET AL DATE: 17-JUL-87 "REPORT OF A SINGLE RISING-DOSE STUDY AND A MULTIPLE-DOSE EXTENDED-TREATMENT STUDY CONDUCTED TO ASSESS THE SAFETY, PHARMACOLOGICAL ACTIVITY, ADMINISTERED TO PATIENTS WITH CONGESTIVE HEART FAILURE (PROTOCOLS 906-7 AND 906-9)"		
31-JUL-87	382	INFORMATION AMENDMENT
CONTENT:		
REVISED PAGE RR 745-00441 PG. 11 DATE: 21-JUL-87		
31-JUL-87	383	PROTOCOL AMENDMENTS
CONTENT:		
AMENDMENT NO. 1 PR. 906-226-2 DATE: 30-APR-87 PROVIDES FOR THE RADIONUCLIDE ASSESSMENT TO BE MEASURED AT BOTH REST AND EXERCISE AND SCHEDULE AND ADDITIONAL MORE COMPREHENSIVE ASSESSMENT TO QUALITY OF LIFE TO BE PERFORMED AT THE LAST VISIT		
AMENDMENT NO. 2 PR. 906-226-5 DATE: 12-MAY-87 THE DOUBLE-BLIND MEDICATION WILL NOT BE DISPENSED AT VISIT 13 - OPEN LABEL MEDICATION WILL BE DISPENSED.		
31-JUL-87	384	PROTOCOL AMENDMENT
CONTENT:		
AMENDMENT NO. 6 PRS. 906-77, 78, 205, 218 AND 233-2 DATE: 10-JUN-87 ADDS AN EVALUATION OF HEMODYNAMIC FUNCTION AT THE END OF ONE YEAR OF OPEN-LABEL AND ALSO INCREASES THE DURATION OF THE OPEN-LABEL PHASE TO 24 MONTHS.		

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DOC DATE	SER/SUPPL NO	TITLE
01-SEP-87	385	ANNUAL REPORT
CONTENT:		CUTOFF DATE: 31-JUL-87
01-SEP-87	386	INFORMATION AMENDMENT
CONTENT:		REVISED PAGE RR X 720-02277 PG. 5 DATE: 17-AUG-87
01-SEP-87	387	INFORMATION AMENDMENT
CONTENT:		RR X-720-02327 AUTHOR: FRANK, G.J. ET AL DATE: 24-AUG-87 "REPORT OF A MULTICENTER, DOUBLE-BLIND, PLACEBO- CONTROLLED, 12-WEEK STUDY COMPARING THE EFFICACY AND SAFETY OF TWICE-DAILY (BID) AND ONCE-DAILY (QD) DOSES OF ORALLY ADMINISTERED QUINAPRIL HYDROCHLORIDE (CI-906) IN PATIENTS WITH HYPERTENSION"
10-SEP-87	388	LETTER RE: CONFIRMATION OF MEETING
CONTENT:		LETTER TO: LIPICKY, RAYMOND J., M.D. RE: CONFIRMING MEETING WITH FDA ON 6-OCT-87 AT 10:00 AM TO DISCUSS QUINAPRIL HYDROCHLORIDE AND HYDROCHLOROTHIAZIDE CLINICAL AND PRE-CLINICAL TOXICOLOGICAL PROGRAMS.
10-SEP-87	389	PROTOCOL AMENDMENT
CONTENT:		AMENDMENT NO. 1 PR. 906-249-0 ADDS A SECOND OBJECTIVE TO THE STUDY: TO ASSESS THE INFLUENCE OF QUINAPRIL ON HEPATIC DRUG OXIDIZING CAPACITY IN MAN.
18-SEP-87	390	PR. 906-257-0
18-SEP-87	391	INFORMATION AMENDMENT
CONTENT:		RR 250-01507 AUTHOR: ROGERS, S.C. ET AL DATE: 18-AUG-87 "13 WEEK DAILY REPEATED DOSE ORAL TOXICITY STUDY OF CI-955 IN RATS"

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DOC DATE	SER/SUPPL NO	TITLE
02-OCT-87	392	PR. 906-244-0
02-OCT-87	393	INFORMATION AMENDMENT
CONTENT:		
RR 745-01155		
AUTHOR: MCGUIRE, E.J.		
DATE: 9-SEP-87		
"TWO-YEAR CARCINOGENICTY STUDY OF CI-906 IN MICE"		
19-OCT-87	394	INFORMATION AMENDMENT
CONTENT:		
RR 764-00856		
AUTHOR: OLSON, S.C. ET AL		
DATE: 2-SEP-87		
"CLINICAL DOSE PROPORTIONALITY STUDY OF QUINAPRIL (CI-906) AND ITS ACTIVE METABOLITE (CI-928) FOLLOWING 2.5 MG TO 80 MG SINGLE CAPSULES DOSES OF QUINAPRIL, PROTOCOL 906-191"		
RR 764-00870		
AUTHOR: OLSON, S.C. ET AL		
DATE: 6-OCT-87		
"EFFECT OF QUINAPRIL ON WARFARIN-INDUCTED REDUCTION IN PROTHROMBIN COMPLEX ACTIVITY IN HEALTHY SUBJECTS - PROTOCOL 906-235"		
19-OCT-87	395	INFORMATION AMENDMENT
CONTENT:		
RR 745-01156		
AUTHOR: KRISHNA, G. ET AL		
DATE: 14-SEPT-87		
"MOUSE MICRONUCLEUS STUDY OF CI-906"		
RR 745-01168		
AUTHOR: KROPKO, M.L. ET AL		
DATE: 14-SEP-87		
"IN VITRO CHROMOSOMAL ABERRATION ASSAY OF CI-906 IN V79 CHINESE HAMSTER LUNG CELLS"		
19-OCT-87	396	INFORMATION AMENDMENT
CONTENT:		
RR 250-01510		
AUTHOR: ROGERS, S.R. ET AL		
DATE: 10-SEP-87		
"13 WEEK ORAL TOXICITY STUDY OF CI-955 IN BEAGLE DOGS"		

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DOC DATE	SER/SUPPL NO	TITLE
29-OCT-87	397	LETTER RE: CHEMISTRY, MANUFACTURING AND CONTROL
CONTENT:		LETTER TO: DIVISION OF CARDIO-RENAL RR 710-00431 RE: UPDATED CHEMISTRY, MANUFACTURING AND CONTROLS DATA.
29-OCT-87	398	PR. 906-241 CENTERS 3, 4, 5, 6, 7, 8 AND 17
29-OCT-87	398	NEW SUB-INVESTIGATOR
CONTENT:		PR. 906-250-2 LLOYD, DOUGLAS, M.D.
05-NOV-87	399	PR. 906-241 CENTERS 2, 9, 10, 11, 12, 21, 24, 27 AND 30
05-NOV-87	400	PROTOCOL AMENDMENT
CONTENT:		AMENDMENT NO. 6 PRS. 906-64, 65, 66, 67, 68, 72, 73, 75, 79, 204, AND 233-5 DATE: 13-MAR-87 ADDS AN EVALUATION OF HEMODYNAMIC FUNCTION AT THE END OF ONE YEAR OF OPEN LABEL AND ALSO INCREASES THE DURATION OF THE OPEN LABEL PHASE TO 24 MONTHS.
12-NOV-87	401	PRS. 906-241-18, -227 CENTERS 30 & 31, -253-2/PR. AMENDMENT
CONTENT:		AMENDMENT NO. 1 PR. 906-253-1 DATE: NONE VASODILATORS USED IN THE TREATMENT OF HYPERTENSION ARE FORBIDDEN AND THAT RENAL FUNCTION EVALUATION WILL BE CARRIED OUT AT THE 4TH WEEK OF ACTIVE TREATMENT.
19-NOV-87	402	INFORMATION AMENDMENT/PROTOCOL AMENDMENT/ADDENDUM
CONTENT:		REVISED PAGE RR 745-00479 PG. 13 DATE: 5-NOV-87  REVISED PAGE RR 745-00608 PG. 2 DATE: 5-NOV-87  REVISED PAGE RR 745-00749 PG. 2 DATE: 5-11-87  AMENDMENT NO. 4 PR. 906-71

DATE: 10-JUN-87

ADDS AN EVALUATION OF HEMODYNAMIC FUNCTION AT THE  
END OF ONE YEAR OF OPEN LABEL AND ALSO INCREASES  
THE DURATION OF THE OPEN LABEL PHASE TO 24  
MONTHS.

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19-NOV-87 402 INFORMATION AMENDMENT/PROTOCOL AMENDMENT/ADDENDUM-CONTINUED  
CONTENT:

ADDENDUM NO. 1  
PR. 906-258-1  
DATE: NONE  
VASODILATORS USED IN THE TREATMENT OF HYPERTENSION  
ARE FORBIDDEN AND THAT RENAL FUNCTION EVALUATION  
WILL BE CARRIED OUT AT THE 4TH WEEK OF ACTIVE  
TREATMENT.

19-NOV-87 403 PR. 906-241 CENTERS 16, 20 AND 28, PR. 906-258-4

19-NOV-87 404 INFORMATION AMENDMENT  
CONTENT:

RR 720-02337  
AUTHOR: FRANK, G.J. ET AL  
DATE: 6-NOV-87  
"A 28-WEEK PARALLEL GROUP DOUBLE-BLIND DOSE-  
RANGING STUDY OF QUINAPRIL (CI-906) IN THE  
TREATMENT OF MILD TO MODERATE ESSENTIAL  
HYPERTENSION (PROTOCOL 9-007)"

RR 724-00079  
AUTHOR: FRANK, G.J. ET AL  
DATE: 6-NOV-87  
"A SINGLE, RISING-DOSE TRIAL TO ASSESS THE SAFETY,  
PHARMACOLOGICAL ACTIVITY, AND PHARMACOKINETICS OF  
ORALLY ADMINISTERED QUINAPRIL IN PATIENTS WITH  
CONGESTIVE HEART FAILURE (PROTOCOL 906-61  
(P.254))"

30-NOV-87 405 INFORMATION AMENDMENT  
CONTENT:

RR 250-01515  
AUTHOR: MACALLUM, G.E. ET AL  
DATE: 9-NOV-87  
"ACUTE INTRAVENOUS TOXICITY STUDY OF CI-906 (PD  
109452-2) IN RATS"

RR 250-01516  
AUTHOR: MACALLUM, G.E. ET AL  
DATE: 9-NOV-87  
"ACUTE INTRAVENOUS TOXICITY STUDY OF CI-906 (PD  
109452-2) IN MICE"

30-NOV-87 406 INFORMATION AMENDMENT  
CONTENT:

RR MEMO-720-02350  
AUTHOR: FRANK, G.J. ET AL  
DATE: 12-NOV-87  
"REPORT OF 24-HOUR BLOOD PRESSURE MONITORING AND  
ASSESSMENT OF URINARY PROTEIN EXCRETION DURING A  
DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY COMPARING  
THE EFFICACY OF ONCE- OR TWICE-DAILY QUINAPRIL  
HYDROCHLORIDE WITH THAT OF Captopril"



ADMINISTERED THREE TIMES A DAY (906-124)  
(SUPPLEMENT TO RR-X-720-02346)"

RR 724-00082

AUTHOR: FRANK, G.J. ET AL

DATE: 19-NOV-87

"A SINGLE, RISING-DOSE TRIAL TO ASSESS THE SAFETY  
AND PHARMACOLOGICAL ACTIVITY OF ORALLY  
ADMINISTERED QUINAPRIL IN PATIENTS WITH  
CONGESTIVE HEART FAILURE (PROTOCOL 906-50  
(P.239))"

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30-NOV-87 406 INFORMATION AMENDMENT - CONTINUED  
CONTENT:

RR MEMO-764-00857

AUTHOR: FRANK, G.J. ET AL

DATE: 19-NOV-87

"SINGLE AND MULTIPLE ORAL DOSE PHARMACOKINETICS  
OF QUINAPRIL (CI-906) AND ITS ACTIVE METABOLITE  
(CI-928) IN YOUNG AND ELDERLY VOLUNTEERS,  
PROTOCOL 906-223"

RR 764-00861

AUTHOR: ALSON, S.C. ET AL

DATE: 29-OCT-87

"SINGLE ORAL DOSE PHARMACOKINETICS OF QUINAPRIL  
(CI-906) AND ITS ACTIVE METABOLITE (CI-928) IN  
PATIENTS WITH HEPATIC IMPAIRMENT SECONDARY TO  
ALCOHOL-INDUCED CIRRHOSIS - PROTOCOL 9-032-0"

30-NOV-87 406 INFORMATION AMENDMENT - CONTINUED  
CONTENT:

RR 764-000867

AUTHOR: OLSON, S.C. ET AL

DATE: 2-OCT-87

"PHARMACOKINETIC DISPOSITION OF <sup>14</sup>C-QUINAPRIL AND  
ITS ACTIVE METABOLITE, CI-928, AFTER SINGLE AND  
MULTIPLE ORAL DOSES OF QUINAPRIL TO HEALTHY  
VOLUNTEERS, PROTOCOL 906-60"

RR 764-000872

AUTHOR: OLSON, S.C. ET AL

DTE: 2-OCT-87

"EFFECT OF MAGNESIUM-CONTAINING QUINAPRIL TABLETS  
ON THE SINGLE-DOSE PHARMACOKINETICS OF  
TETRACYCLINE IN HEALTHY VOLUNTEERS, PROTOCOL  
906-237"

30-NOV-87 407 INFORMATION AMENDMENT  
CONTENT:

RR 4301-00015

AUTHOR: BAKOVIC-ALT, R. ET AL

DATE: 18-AUG-87

"REPORT OF A MULTICENTER, DOUBLE-BLIND, PLACEBO  
CONTROLLED, 12-WEEK STUDY DETERMINING THE  
EFFICACY AND SAFETY OF TWICE-A-DAY, ORALLY  
ADMINISTERED QUINAPRIL 5 MG, 10 MG AND 20 MG IN  
THE TREATMENT OF CONGESTIVE HEART FAILURE  
(CT 891-140)"

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30-NOV-87	408	INFORMATION AMENDMENT
CONTENT:		RR MEMO-4301-00032 AUTHOR: BAKOVIC-ALT, R. ET AL DATE: 11-SEP-87 "REPORT OF A ONE-YEAR OPEN-LABEL MULTICENTER STUDY FOLLOWING A 12-WEEK, DOUBLE-BLIND, PLACEBO CONTROLLED STUDY TO DETERMINE THE EFFICACY AND SAFETY OF ORAL ADMINISTERED QUINAPRIL HYDROCHLORIDE (CI-906) IN PATIENTS WITH CONGESTIVE HEART FAILURE (INTERIM ANALYSIS, CT 891-140 FF)"
01-DEC-87	409	MINUTES OF FDA MEETING
CONTENT:		DATE: 6-OCT-87 DISCUSSED THE PHASE 2/3 CLINICAL PROGRAM AND NDA FOR THE COMBINATION OF QUINAPRIL (CI-906 AND HYDROCHLOROTHIAZIDE TO BE USED AS ANTIHYPERTENSIVE THERAPY.
15-DEC-87	410	INFORMATION AMENDMENT
CONTENT:		RR 745-01173 AUTHOR: ANDERSON, JA. ET AL DATE: 13-NOV-87 "104-WEEK CARCINOGEN BIOASSAY WITH CI-906 IN RATS"
15-DEC-87	411	INFORMATION AMENDMENT
CONTENT:		RR 720-02364 AUTHOR: FRANK, G.J. ET AL DATE: 17-NOV-87 INTERIM REPORT OF THE OPEN-LABEL PHASE OF A MULTICENTER, FIXED-DOSE, DOUBLE-BLIND, PLACEBO- CONTROLLED STUDY TO DETERMINE EFFICACY AND SAFETY OF ORALLY ADMINISTERED CI-906 IN PATIENTS WITH MILD TO MODERATE HYPERTENSION (PROTOCOL 906-12, 906-13 AND 905-15 THRU 906-22)"
15-DEC-87	412	INFORMATION AMENDMENT
CONTENT:		RR 740-02311 AUTHOR: DAVIS, R.E. DATE: 3-DEC-87 "EFFECT OF PD 109452 (CI-906), AND ANGIOTENSION CONVERTING ENZYME INHIBITOR (ACE) ON BODY TEMPERATURE AND SURVIVAL TIME UNDER NORMOBARIC HYPOXIA IN MICE"
		RR 740-02312 AUTHOR: DAVIS, R.E. DATE: 3-DEC-87 "EFFECT OF CI-906 (PD 109452), AND ANGIOTENSION

ALTERNATION PERFORMANCE IN RATS"

REVISED PAGES RR 745-01168

PGS. 3, 9, 10, 159, 163, 182, 184 AND 186

DATE: 24-NOV-87

CROSS REFERENCE: 395

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15-DEC-87	413	PR. 906-241 CENTERS 13, 14 AND 15
22-DEC-87	414	INFORMATION AMENDMENT
CONTENT:		
RR 720-02334 AUTHOR: FRANK, G.J. ET AL DATE: 25-NOV-87 "INTERIM REPORT OF THE OPEN-LABEL PHASE OF A MULTICENTER, PLACEBO-CONTROLLED STUDY TO DETERMINE THE COMPARATIVE EFFICACY AND SAFETY OF ORALLY-ADMINISTERED QUINAPRIL HYDROCHLORIDE (CI-906), CHLORTHALIDONE, AND QUINAPRIL PLUS CHLORTHALIDONE IN PATIENTS WITH MILD TO MODERATE HYPERTENSION (RR X-720-02185) (PROTOCOLS 906-30 TO 38, -41 TO 46)"		
22-DEC-87	415	INFORMATION AMEDMENT
CONTENT:		
RR X-720-02318 AUTHOR: FRANK, G.J. ET AL DATE: 19-NOV-87 "INTERIM REPORT OF THE OPEN-LABEL PHASE OF A MULTICENTER, DOUBLE-BLIND, 12-WEEK STUDY COMPARING THE EFFICACY AND SAFETY OF QUINAPRIL HYDROCHLORIDE (CI-906) WITH CAPTOPRIL IN THE TREATMENT OF MODERATE TO SEVERE HYPERTENSION (PROTOCOLS 906-82 TO 906-86, 906-89 TO 906-91, 906-93, 906-95, 906-96)"		
22-DEC-87	416	PRS. 906-258-03, 906-241-14X, 906-241-32
22-DEC-87	417	INFORMATION AMENDMENT
CONTENT:		
RR 720-02369 AUTHOR: FRANK, G.J. ET AL DATE: 24-NOV-87 "INTERIM REPORT OF THE OPEN-LABEL PHASE OF A MULTICENTER, DOUBLE-BLIND STUDY TO COMPARE THE EFFICACY AND SAFETY OF ORALLY ADMINISTERED QUINAPRIL HYDROCHLORIDE (CI-906) TO ORALLY ADMINISTERED CAPTOPRIL IN PATIENTS WITH MILD TO MODERATE HYPERTENSION (PROTOCOLS 906-114 TO 906-131, 906-133, 906-134, 906-137, 906-138)"		
22-DEC-87	418	INFORMATION AMENDMENT
CONTENT:		
REVISED PAGE RR 764-00870 PG. 6/7 DATE: 9-NOV-87 CROSS REFERENCE: SERIAL #394  RR 764-00916 AUTHOR: MICHNIEWICZ, B. ET AL DATE: 10 OCT 87		

"METABOLIC DISPOSITION OF <sup>14</sup>QUINAPRIL IN RATS"

RR 764-00917

AUTHOR: MICHNIEWICZ, B. ET AL.

DATE: 30-NOV-87

"CHARACTERIZATION OF QUINAPRIL METABOLITES IN  
URINE OF MAN AND DOG FOLLOWING ADMINISTRATION OF  
<sup>14</sup>QUINAPRIL"

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29-DEC-87 419 INFORMATION AMENDMENT  
CONTENT:

RR X-720-02346  
AUTHOR: FRANK, G.J. ET AL  
DATE: 11-DEC-87  
"A MULTICENTER, DOUBLE-BLIND, PLACEBO-CONTROLLED,  
12-WEEK STUDY TO COMPARE THE EFFICACY AND SAFETY  
OF ORALLY ADMINISTERED QUINAPRIL HYDROCHLORIDE  
(CI-906) TO ORALLY ADMINISTERED CAPTOPRIL IN  
PATIENTS WITH MILD TO MODERATE ESSENTIAL  
HYPERTENSION (PROTOCOL 906-114 TO 906-131,  
906-133, 906-124, 906-136 TO 906-138)"

29-DEC-87 420 INFORMATION AMENDMENT  
CONTENT:

REVISED PAGES RR X-720-02185  
COMPLETE REPORT  
DATE: 4-DEC-87  
CROSS REFERENCE: SERIAL #353

05-JAN-88 421 INFORMATION AMENDMENT  
CONTENT:

RR 764-00887  
AUTHOR: HORVATH, A.M. ET AL  
DATE: 2-NOV-87  
"SINGLE-DOSE BIOEQUIVALENCE STUDY COMPARING  
QUINAPRIL 5- AND 40-MG MARKET-IMAGE TABLETS AND  
QUINAPRIL 20-MG CAPSULES IN HEALTHY VOLUNTEERS -  
PROTOCOL 906-230"  
  
RR MEMO-764-00915  
AUTHOR: OLSON, S.C. ET AL  
DATE: 20-NOV-87  
"MULTIPLE ORAL DOSE PHARMACOKINETIC OF QUINAPRIL  
(CI-906) AND ITS ACTIVE METABOLITE (CI-928) IN  
RENAL FAILURE - PROTOCOL 906-AE INTERIM ANALYSIS"

05-JAN-88 422 INFORMATION AMENDMENT  
CONTENT:

RR 720-02349  
AUTHOR: FRANK, G. ET AL  
DATE: 20-NOV-87  
"REPORT OF A COMPARATIVE PHARMACOKINETIC STUDY OF  
ONCE-DAILY ORALLY ADMINISTERED QUINAPRIL  
HYDROCHLORIDE (CI-906) IN YOUNG SUBJECTS AND  
ELDERLY PATIENTS WITH MILD TO MODERATE  
HYPERTENSION (906-223)"

RR 724-00081  
AUTHOR: FRANK G.J., ET AL  
DATE: 30-NOV-87  
"A 16-WEEK, MULTIPLE-DOSE STUDY OF THE SAFETY,  
PHARMACOLOGICAL ACTIVITY, AND PHARMACOKINETICS OF  
ORALLY ADMINISTERED QUINAPRIL IN PATIENTS WITH  
CONGESTIVE HEART FAILURE (PROTOCOL 906-62  
(2-255))"

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05-JAN-88	423	INFORMATION AMENDMENT
CONTENT:		
RR X-720-02345		
AUTHOR: FRANK, G.J.		
DATE: 25-NOV-87		
"INTERIM REPORT OF THE OPEN-LABEL PHASE OF A MULTICENTER, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO DETERMINE EFFICACY AND SAFETY OF TWICE- DAILY (BID) AND ONCE-DAILY (QD) ORAL DOSES OF QUINAPRIL HYDROCHLORIDE (CI-906) IN PATIENTS WITH HYPERTENSION (PROTOCOLS 906-11, 906-48, 906-49 AND 906-906-52 TO 906-59)"		
12-JAN-88	424	INFORMATION AMENDMENT
CONTENT:		
RR 720-02338		
AUTHOR: FRANK, G.J. ET AL		
DATE: 10-DEC-87		
"A MULTICENTER, 28-WEEK, PARALLEL GROUP, RANDOMIZED, DOUBLE-BLIND, DOSE-RANGING STUDY OF QUINAPRIL (CI-906) VERSUS ENALPRIL IN THE TREATMENT OF MILD TO MODERATE ESSENTIAL HYPERTENSION (PROTOCOL WLI-9-003-4)"		
12-JAN-88	425	INFORMATION AMENDMENT
CONTENT:		
RR 4301-00023		
AUTHORS: WOELFING, A. LILIENTHAL, H.		
DATE: 11-SEP-87		
"REPORT OF A MULTICENTER, DOUBLE-BLIND, 28-WEEK STUDY COMPARING THE EFFICACY AND SAFETY OF TWICE- A-DAY ORALLY ADMINISTERED QUINAPRIL HYDROCHLORIDE WITH ENALAPRIL IN PATIENTS WITH MILD TO MODERATE HYPERTENSION (CT 890-200)"		
12-JAN-88	426	INFORMATION AMENDMENT
CONTENT:		
RR: 740-02345		
AUTHORS: STEFFEN, R.P. ELDON, C.M.		
DATE: 11-DEC-87		
"EFFECT OF ANGIOTENSIN-CONVERTING ENZYME (ACE) INHIBITORS ON RENAL AND PERIPHERAL HEMODYNAMICS AND URINE OUTPUT IN ANESTHETIZED DOG"		
RR 740-02378		
AUTHOR: SINGER, R. ET AL		
DATE: 16-DEC-87		
"EFFECTS OF QUINAPRIL ON BLOOD PRESSURE AND HEART RATE IN DIURETIC-TREATED RENAL HYPERTENSIVE DOGS"		

REVISED PAGE RR MEMO-764-00916

PG. 2/3

DATE: 23/DEC-87



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12-JAN-88 427 PR 906-241-19/INFORMATION AMENDMENT  
CONTENT:

REVISED PAGES RR 724-00039  
PGS. 6/7 AND 8/9

RR 724-00083  
AUTHOR: FRANK, G.J. ET AL  
DATE: 18-DEC-87  
"A 16-WEEK, MULTIPLE-DOSE STUDY OF THE SAFETY,  
PHARMACOLOGICAL ACTIVITY, AND PHARMACOKINETICS OF  
ORALLY ADMINISTERED QUINAPRIL IN PATIENTS WITH  
CONGESTIVE HEART FAILURE (PROTOCOL 906-51 P.240)"

19-JAN-88 428 INFORMATION AMENDMENT  
CONTENT:

REVISED PAGE RR 764-00867  
PG. 2/3  
DATE: 5-JAN-88

RR MEMO-745-01206  
AUTHOR: ANDREWS, L.K.  
DATE: 22-DEC-87  
"TWO-YEAR CARCINOGENICITY STUDY OF CI-906 IN MICE:  
A REVIEW OF HISTOPATHOLOGIC CHANGES IN THE  
KIDNEY"

19-JAN-88 429 INFORMATION AMENDMENT  
CONTENT:

RR 740-02354  
AUTHORS: WEISHAAR, R.  
ESSENBERG, A.  
DATE: 4-JAN-88  
"EFFECT OF PD 109489-2K AND REFERENCE AGENTS ON  
THE ACTIVITY OF ANGIOTENSIN CONVERTING ENZYME"

RR 740-02355  
AUTHORS: WEISHAAR, R.E.  
ESSENBERG, A.D.  
DATE: 4-JAN-88  
"EFFECT OF PD 109478-2 AND REFERENCE AGENTS ON THE  
ACTIVITY OF ANGIOTENSIN CONVERTING ENZYME"

RR 740-02356  
AUTHOR: WEISHAAR, R.E.  
ESSENBERG, A.D.  
DATE: 4-JAN-88  
"EFFECT OF PD 126130 AND REFERENCE AGENTS ON THE  
ACTIVITY OF ANGIOTENSIN CONVERTING ENZYME"

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19-JAN-88 429 INFORMATION AMENDMENT - CONTINUED  
CONTENT:

RR 740-02357

AUTHORS: WEISHAAR, R.E.  
ESSENBERG, A.D.

DATE: 4-JAN-88

"EFFECT OF PD 118854 AND REFERENCE AGENTS ON THE  
ACTIVITY OF ANGIOTENSIN CONVERTING ENZYME"

19-JAN-88 430 INFORMATION AMENDMENT  
CONTENT:

RR 4301-00030

AUTHORS: FRIEDRICH, R.  
SAUERMAN, W.

DATE: 31-AUG-87

"REPORT OF A DOUBLE-BLIND, FIXED-DOSE, PLACEBO-  
CONTROLLED, 2-WEEK STUDY OF THE EFFICACY AND  
SAFETY OF ORALLY ADMINISTERED QUINAPRIL  
HYDROCHLORIDE (CI-906) IN PATIENTS WITH MILD TO  
MODERATE HYPERTENSION UNDER EXERCISE STRESS TEST  
CONDITIONS"

19-JAN-88 431 INFORMATION AMENDMENT  
CONTENT:

RR X-720-02367

AUTHOR: FRANK, G.J. ET AL  
DATE: 14-DEC-87

"INTERIM SUMMARY REPORT OF THE OPEN-LABEL PHASE  
OF FOUR MULTICENTER, DOUBLE-BLIND PLACEBO-  
CONTROLLED STUDIES TO DETERMINE THE EFFICACY AND  
SAFETY OF ORALLY ADMINISTERED QUINAPRIL  
HYDROCHLORIDE (CI-906) IN PATIENTS WITH ESSENTIAL  
HYPERTENSION (PROTOCOLS 906-12, 906-13, 906-15  
THROUGH 906-22, 906-30 THROUGH 906-38, 906-41  
THROUGH 906-46, 906-82 THROUGH 906-86, 908-89  
THROUGH 906-91, 906-93, 906-95, 906-96, 906-114  
THROUGH 906-124, 906-126 THROUGH 906-131, 906-133  
906-134, 906-137 AND 906-138)"

26-JAN-88 432 PR. 906-241-34 & X-34/INFORMATION AMENDMENT/PROTOCOL AMEND.  
CONTENT:

REVISED PAGE RR 764-00131

PG. 11/12

DATE: 7-JAN-88

AMENDMENT NO. 3

PR. 906-123

DATE: 15-APR-87

ALLOWS FOR CONTINUATION OF OPEN-LABEL TREATMENT  
FOR AN ADDITIONAL 12 MONTHS.

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26-JAN-88 433 INFORMATION AMENDMENT  
CONTENT:

REVISED PAGES X-720-02147  
COMPLETE REPORT  
DATE: 8-DEC-87  
CROSS REFERENCE: SERIAL #314

26-JAN-88 434 INFORMATION AMENDMENT  
CONTENT:

RR 720-02332  
AUTHOR: FRANK. G.J. ET AL  
DATE: 22-DEC-87  
"OVERALL REPORT OF A MULTICENTER, DOUBLE-BLIND,  
12-WEEK STUDY COMPARING THE EFFICACY AND SAFETY  
OF QUINAPRIL HYDROCHLORIDE (CI-906) WITH  
CAPTOPRIL IN THE TREATMENT OF MODERATE TO SEVERE  
HYPERTENSION (PROTOCOLS 906-82 TO 87, -89 TO 91,  
-93, -95, -96)"

03-FEB-88 435 INFORMATION AMENDMENT  
CONTENT:

RR 4301-00025  
AUTHOR: WOELFING, A. ET AL  
DATE: 11-SEP-87  
"REPORT OF A MULTICENTER, DOUBLE-BLIND PARALLEL  
28-WEEK STUDY COMPARING THE EFFICACY AND SAFETY  
OF TWICE A DAY ORALLY ADMINISTERED QUINAPRIL  
HYDROCHLORIDE WITH TWICE A DAY ORALLY  
ADMINISTERED ENALAPRIL WHEN BOTH GIVEN IN  
ADDITION TO ONCE A DAY CHLORTHALIDONE IN  
PATIENTS WITH MODERATE TO SEVERE HYPERTENSION  
(CT 890-170)"

03-FEB-88 436 PRS. 906-241-1 AND 906-241X-1/INFORMATION AMENDMENT  
CONTENT:

REVISED PAGES RR 720-02337  
PGS. 22 AND 23  
DATE: 18-JAN-88

03-FEB-88 437 SAFETY REPORT  
CONTENT:

PATIENT NO.: 6 (SOP)  
PR. 906-68  
AE: DEATH - CARDIAC ARREST  
NOT DRUG RELATED.  
FOLLOW-UP REPORT - SERIAL #348  
AE 001-0906-870013-01

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10-FEB-88 438 INFORMATION AMENDMENT

CONTENT:

REVISED PAGES RR 4301-0023  
PGS. 21, 78, 79, 95, 266H/2261, 226J/267 AND 1932  
THROUGH 1957  
DATE: 18-JAN-88

10-FEB-88 439 INFORMATION AMENDMENT

CONTENT:

REVISED PAGES RR X-720-02327  
COMPLETE REPORT  
DATE: 1-DEC-87  
CROSS REFERENCE: SERIAL #387

24-FEB-88 440 INFORMATION AMENDMENT

CONTENT:

REVISED PAGE RR 720-02147  
PG. 23B  
DATE: 16-FEB-88

REVISED PAGE RR X-720-02185  
PG. 5  
DATE: 15-FEB-88

REVISED PAGE 720-02332  
PGS. 2 AND 5  
DATE: 16-FEB-88

REVISED PAGES RR X-720-02345  
PGS. 3, 4 AND 35  
DATE: 19-FEB-88

REVISED PAGE RR MEMO-720-02350  
PG. 2  
DATE: 18-FEB-88

24-FEB-88 441 INFORMATION AMENDMENT

CONTENT:

REVISED PAGES RR 720-02369  
PGS. 2, 16, 965 THROUGH 980  
DATE: 17-FEB-88

REVISED PAGE RR 724-00051  
PG. 2  
DATE: NONE

REVISED PAGES RR X-724-00072  
PG. 9  
DATE: 15-FEB-88

REVISED PAGE RR 724-00081  
PGS. 3, 5, 10 AND 22  
DATE: 16-FEB-88

REVISED PAGE RR 745-00767

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24-FEB-88	442	INFORMATION AMENDMENT
CONTENT:		
REVISED PAGES RR 720-02337		
PGS. COVER SHEET, 2, 3, 4, 7, 8 14, 16, 21, 24-27,		
30, 33-36, 52 AND 54		
DATE: 22-FEB-88		
02-MAR-88		LETTER RE: REQUEST FOR INFORMATION
CONTENT:		
LETTER FROM: LIPICKY, RAYMOND J., M.D.		
RE: REQUEST FOR ADDITIONAL MANUFACTURING AND		
CONTROLS DATA.		
04-MAR-88	443	PR. 906-241-31/NEW SUB-INVESTIGATOR
CONTENT:		
PR. 906-241-32		
DUENSING, DAVID T., M.D.		
04-MAR-88	444	PR. 906-267-0
04-MAR-88	445	INFORMATION AMENDMENT
CONTENT:		
REVISED PAGES RR 762-00556		
PGS. 160 AND 161		
REVISED PAGES RR 720-02364		
PGS. 2 AND 20		
DATE: 15-FEB-88		
REVISED PAGES RR X-720-02346		
PGS. 3, 4, 5, 22, 75 AND 76		
DATE: 25-FEB-88		
REVISED PAGES RR 720-02334		
PGS. 2, 3, 16 AND 26		
DATE: 25-FEB-88		
04-MAR-88	446	INFORMATION AMENDMENT
CONTENT:		
REVISED PAGES RR MEMO-4301-00032		
PGS. 4, 18 AND 19		
REVISED PAGES RR 4301-00023		
PGS. 3, 4, 5, 7, 8, 20, 30, 64, 74, 75, 91 AND 106		
REVISED PAGE RR 724-00082		
PG. 10		

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04-MAR-88 447 INFORMATION AMENDMENT

CONTENT:

REVISED PAGES RR X-720-02367  
PGS. TITLE PAGE, 2, 5, 8, 14 AND 46  
DATE: 26-FEB-88

REVISED PAGES RR 724-00083  
PGS. 3, 4, 8, 9, 10, 11 AND 20  
DATE: 26-FEB-88

24-MAR-88 448 PR. 906-283-0

24-MAR-88 449 PROTOCOL AMENDMENT

CONTENT:

AMENDMENT NO. 3  
PRS. 906-116, 117, 121, 122, 124, 126, 128, 129,  
130 AND 131  
DATE: 15-APR-87  
ALLOWS FOR THE CONTINUATION OF OPEN-LABEL  
TREATMENT FOR AN ADDITIONAL 12 MONTHS (TOTAL 24  
MONTHS).

AMENDMENT NO. 4  
PRS. 906-31, 34, 35, 36, 37, 42, 43, 45, 82, 83,  
84, 85, 86, 89, 90, 91, 96 AND 124  
DATE: 15-APR-87  
ALLOWS FOR THE CONTINUATION OF OPEN-LABEL  
TREATMENT FOR AN ADDITIONAL 12 MONTHS (TOTAL 24  
MONTHS).

AMENDMENT NO. 5  
PRS. 906-33 AND 44  
DATE: 15-APR-87  
ALLOWS FOR THE CONTINUATION... (TOTAL 24 MONTHS).

28-MAR-88 450 LETTER RE: MEETING REQUEST

CONTENT:

LETTER TO: LIPICKY, RAYMOND J., M.D.  
RE: PRE-NDA MEETING REQUEST:  
1) DRAFT PACKAGE INSERT.  
2) OVERVIEW OF THE CLINICAL PROGRAM.

12-APR-88 451 PRS. 906-241-29 & X-29, 35 & X-35

12-APR-88 452 PR. 906-258-2

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12-APR-88 453 PROTOCOL AMENDMENT

CONTENT:

AMENDMENT NO. 3  
PR. 906-226-2  
DATE: 27-NOV-87  
CHANGES THE EXERCISE TIME AND EXERCISE STAGES.

12-APR-88 454 INFORMATION AMENDMENT

CONTENT:

RR 764-00970  
AUTHOR: HORVATH, A.M. ET AL  
DATE: 5-FEB-88  
"CLINICAL DOSE-PROPORTIONALITY STUDY OF QUINAPRIL  
(CI-906) AND ITS ACTIVE METABOLITE (CI-928)  
FOLLOWING SINGLE 2.5-MG. TO 80-MG. TABLET DOSES  
OF QUINAPRIL, PROTOCOL 906-259"

22-APR-88 455 LETTER RE: CONFIRMING MEETING

CONTENT:

LETTER TO: LIPICKY, RAYMOND J., M.D.  
RE: CONFIRMATION OF PRE-NDA MEETING ON 6-MAY-88 AT  
10:00 A.M.

09-MAY-88 456 INFORMATION AMENDMENT

CONTENT:

REVISED PAGE RR 720-02349  
COMPLETE REPORT  
DATE: 2-MAR-88

09-MAY-88 457 PROTOCOL AMENDMENT/NEW SUB-INVESTIGATOR

CONTENT:

AMENDMENT NO. 1  
PR. 906-177  
DATE: 2-APR-87  
ADDS AN ASSESSMENT OF QUALITY OF LIFE AT THE LAST  
PLACEBO BASELINE VISIT AND AT THE END OF THE  
DOUBLE-BLIND.

AMENDMENT NO. 4  
PR. 906-226-1  
DATE: NONE  
ALLOWS PATIENTS WHO HAVE PREVIOUSLY PARTICIPATED  
IN PR. 906-256-0 TO PARTICIPATE IN PR. 906-226-1.

PR. 906-226-32  
VAN DE NOBELEN, J.A.E.F.M.

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09-MAY-88 458 LETTER RE: CHEMISTRY, MANUFACTURING & CONTROLS  
CONTENT:

LETTER TO: DIVISION OF CARDIO-RENAL  
RR X-929-00069  
RE: UPDATES OUR MANUFACTURING AND CONTROLS DATA  
FOR THIS FORMULATION.

16-MAY-88 459 PRS. 906-241-25 & X-25/PROTOCOL AMENDMENT  
CONTENT:  
AMENDMENT NO. 2  
PR. 906-241-25

26-MAY-88 460 PR. 906-281-0

26-MAY-88 461 INFORMATION AMENDMENT  
CONTENT:  
RR 764-01014  
AUTHOR: OLSON, S.C. ET AL  
DATE: 8-APR-88  
"MULTIPLE ORAL DOSE PHARMACOKINETICS OF QUINAPRIL  
(CI-906) AND ITS ACTIVE METABOLITE (CI-928) IN  
RENAL FAILURE - PROTOCOL 906-AE"

27-MAY-88 462 LETTER RE: MEETING REQUEST  
CONTENT:  
LETTER TO: LIPICKY, RAYMOND J., M.D.  
RE: REQUEST MEETING TO DISCUSS THE CHEMISTRY,  
MANUFACTURING AND CONTROL ISSUES.

27-MAY-88 463 MINUTES OF FDA MEETING  
CONTENT:  
DATE: 9-MAY-88  
PRE-NDA FDA MEETING

14-JUN-88 464 LETTER RE: REQUEST FOR INFORMATION  
CONTENT:  
LETTER TO: LIPICKY, RAYMOND J., M.D.  
RE: WRITTEN REQUEST FOR COMMENTS ON SPECIFIC ITEMS  
CONCERNING THE NDA.

20-JUN-88 465 INFORMATION AMENDMENT/PR. 906-227-21  
CONTENT:  
RR 740-02456  
AUTHOR: KRAUSE, B.R. ET AL  
DATE: 6-JUN-88  
"EFFECT OF QUINAPRIL, CAPTORPIL, AND ENALAPRIL IN  
FRUCTOS-FED RATS"

RR 740-02383  
AUTHOR: RYAN, M.J. ET AL  
DATE: 7-JUN-88



FIVE-DAY DOSING STUDY IN RENAL HYPERTENSIVE RATS"

RR 740-02484

AUTHOR: RYAN, M.J. ET AL

DATE: 7-JUN-88

"ANTIHYPERTENSIVE ACTIVITY OF QUINAPIRL IN  
HYDROCHLOROTHIAZIDE-TREATED CONSCIOUS  
SPONTANEOUSLY HYPERTENSIVE RATS"

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20-JUN-88 465 INFORMATION AMENDMENT/PR. 906-227-21 - CONTINUED  
CONTENT:

RR 745-01248  
AUTHOR: HURTT, M.E. ET AL  
DATE: 18-MAY-88  
"RAT BONE MARROW CYTOGENETIC STUDY OF CI-906"

01-JUL-88 LETTER RE: FDA REQUEST FOR INFORMATION  
CONTENT:

LETTER FROM: LIPICKY, RAYMOND J., M.D.  
RE: WRITTEN REQUEST FOR ADDITIONAL MANUFACTURING  
AND CONTROLS DATA.

07-JUL-88 466 ANNUAL REPORT  
CONTENT:  
CUTOFF DATE: 1-MAY-88

07-JUL-88 467 PR. 906-273-0

19-JUL-88 468 LETTER RE: MINUTES OF FDA MEETING  
CONTENT:  
LETTER TO: LIPICKY, RAYMOND J., M.D.  
RE: TELEPHONE CONVERSATION: 13-JUN-88 FOLLOW-UP ON  
THE PRE-NDA MEETING.

26-JUL-88 469 PRS. 906-261 AND 906-282/PROTOCOL AMENDMENT  
CONTENT:  
AMENDMENT NO. 7  
PR. 906-64  
DATE: 1-JUN-88  
ALLOWS THE EXTENSION OF THE OPEN-LABEL PHASE  
TO 36 MONTHS.

04-AUG-88 470 PR. 906-293-0

10-AUG-88 471 MINUTES OF FDA MEETING  
CONTENT:  
LETTER TO: LIPICKY, RAYMOND J., M.D.  
MINUTES OF 8-JUL-88 MEETING TO REVIEW CERTAIN  
CHEMISTRY, MANUFACTURING AND CONTROL ISSUES FOR  
THE SUBMISSION OF AN NDA.

26-AUG-88 472 LETTER RE: PROTOCOL CANCELLATION/PROTOCOL AMD/INFOR. AMD.  
CONTENT:  
LETTER TO: LIPICKY, RAYMOND J., M.D.  
PR. 906-273-0  
RE: CANCELLATION OF PROTOCOL  
  
AMENDMENT NO. 1  
PR. 906-273-0

TO MODIFY THE LOWER LIMIT OF MEAN URINARY  
ALBUMIN EXCRETION FROM 70MG PER DAY TO 50MG  
PER DAY.

RR 740-02528

AUTHOR: KRAUSE, B.R. ET AL

DATE: 2-AUG-88

"EFFECT OF ACE INHIBITORS ON PLASMA LIPIDS IN  
NORMAL RATS: CONFIRMATION OF TRIGLYCERIDE-  
LOWERING EFFECT USING ORAL DOSING"

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26-AUG-88 473 INFORMATION AMENDMENT  
CONTENT:

RR 720-02386  
AUTHOR: BERGHOFF, W. ET AL  
DATE: 18-AUG-88  
"REPORT OF A COMPARISON OF QUINAPRIL (CI-906) AND  
CI-928 PLASMA CONCENTRATIONS WITH REDUCTION IN  
DIASTOLIC BLOOD PRESSURE DURING A 12-WEEK DOUBLE-  
BLIND STUDY IN PATIENTS WITH MODERATE TO SEVERE  
HYPERTENSION (PROTOCOL 906-82 THROUGH 906-87,  
906-89 THROUGH 906-91, 906-92, 906-95, AND  
906-96)"

16-SEP-88 474 INFORMATION AMENDMENT/PROTOCOL AMENDMENT  
CONTENT:

RR 740-01519  
AUTHOR: PACE, D.P. ET AL  
DATE: 30-AUG-88  
"HEMODYNAMIC RESPONSES TO QUINAPRIL (CI-906) IN  
CONSCIOUS SODIUM-RESTRICTED FUROSEMIDE-TREATED  
DOGS"

AMENDMENT NO. 8  
PR. 906-64  
CANCELLATION OF THE 3RD YEAR OF OPEN-LABEL.

30-SEP-88 475 PROTOCOL AMENDMENT/NEW PRINCIPAL INVESTIGATOR/PR. 906-295  
CONTENT:

AMENDMENT NO. 8  
PR. 906-68  
DATE: NONE  
CANCELLATION OF THE 3RD YEAR OF OPEN-LABEL.

PR. 906-131  
HAUCH, THOMAS, M.D.

30-SEP-88 476 INFORMATION AMENDMENT  
CONTENT:

RR 720-02388  
AUTHOR: BECKER, M. ET AL  
DATE: 8-SEP-88  
"REPORT OF THE OPEN-LABEL PHASE OF A MULTICENTER  
FIXED-DOSE, DOUBLE-BLIND, PLACEBO-CONTROLLED  
STUDY TO DETERMINE EFFICACY AND SAFETY OF ORALLY  
ADMINISTERED QUINAPRIL HYDROCHLORIDE (CI-906) IN  
PATIENTS WITH MILD TO MODERATE HYPERTENSION  
(PROTOCOL 906-12, 906-13, AND 906-15 TO 906-22)"

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DOC DATE	SER/SUPPL NO	TITLE
14-OCT-88	477	INFORMATION AMENDMENT
CONTENT:		
RR 764-01083 AUTHOR: BERGER, P.J. ET AL DATE: 24-AUG-88 "A VALIDATED GAS CHROMATOGRAPHIC METHOD TO DETERMINE CI-906 AND ITS ACTIVE METABOLITE, CI-928, IN HUMAN URINE"		
RR 764-01094 AUTHOR: OLSON, S.C. ET AL DATE: 31-AUG-88 "COMPARISON AND SUMMARY OF ANALYTICAL METHODS USED TO CHARACTERIZE QUINAPRIL (CI-906) AND ITS ACTIVE METABOLITE, QUINAPRILAT (CI-928), IN CLINICAL PHARMACOKINETIC STUDIES"		
14-OCT-88	477	INFORMATION AMENDMENT - CONTINUED
CONTENT:		
RR 764-01099 AUTHOR: OLSON, S.C. ET AL DATE: 31-AUG-88 "COMPARISON AND SUMMARY OF ANALYTICAL METHODS USED TO CHARACTERIZE QUINAPRIL (CI-906) AND ITS ACTIVE METABOLITES, QUINAPRILAT (CI-928), IN PRE-CLINICAL PHARMACOKINETIC STUDIES"		
14-OCT-88	478	INFORMATION AMENDMENT
CONTENT:		
RR 724-00093 AUTHOR: BECKER, M. ET AL DATE: 1-OCT-88 "REPORT OF A PLACEBO-CONTROLLED 24-HOUR BLOOD PRESSURE MONITORING STUDY OF ONCE AND TWICE DAILY ORAL DOSES OF QUINAPRIL HYDROCHLORIDE (CI-906) IN PATIENTS WITH MILD TO MODERATE HYPERTENSION (PROTOCOL 906-250-1 THROUGH 906-250-3)"		
14-OCT-88	479	PRS. 906-268-1 & 305-0/NEW SUB-INVESTIGATOR/PR. AMENDMENT
CONTENT:		
PR. 906-8 DENBLINDEN, J.L., M.D. GEORGE, B., M.D.  AMENDMENT NO. 1 PR. 906-268 DATE: 15-SEP-88 THE FOLLOWING SECTIONS OF THE PROTOCOL HAVE BEEN CHANGED: 1. A) SECTION IV G8, PAGE 16 B) TABLET 1, PAGE 21 C) APPENDIX 1, SECTION E, PAGE 25 2. PAGE 19, PARAGRAPH 3		

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28-OCT-88 480 PR. 906-263-3/PROTOCOL AMENDMENT/NEW SUB-INVESTIGATOR  
CONTENT:

AMENDMENT NO. 1  
PR. 906-263  
DATE: 18-AUG-88  
ALLOWS PATIENTS TO ENTER THE 24 WEEK OPEN-LABEL  
PHASE AFTER A TWO TO THREE WEEK PLACEBO BASELINE  
PERIOD.

AMENDMENT NO. 2  
PR. 906-263  
DATE: 14-SEP-88  
ALLOWS PATIENTS WITH A HEART RATE OF 55 OR GREATER  
BEATS PER MINUTE TO ENTER THE STUDY.

PR. 906-238-5  
GRIEGO, GENARA, M.D.

28-OCT-88 481 INFORMATION AMENDMENT  
CONTENT:

RR 764-01061  
AUTHOR: OLSON, S.C. ET AL  
DATE: 20-JUL-88  
"A PRELIMINARY ESTIMATE OF THE EFFECTIVE  
ACCUMULATION HALF-LIFE FOR QUINAPRILAT"

28-OCT-88 482 INFORMATION AMENDMENT  
CONTENT:

RR 764-01084  
AUTHOR: HORVATH, A.M. ET AL  
DATE: 25-AUG-88  
"THE PHARMACOKINETICS OF QUINAPRIL HCL AND ITS  
ACTIVE METABOLITE (QUINAPRILAT) IN PATIENTS WITH  
VARYING DEGREES OF RENAL FUNCTION - PROTOCOL  
906-255"

RR MEMO-764-01085  
AUTHOR: HORVATH, A.M. ET AL  
DATE: 26-AUG-88  
"THE PHARMACOKINETICS OF THE DIKETOPIPERAZINE  
METABOLITE OF QUINAPRIL HCL, PD 109488, AND THE  
DIKETOPIPERAZINE METABOLITE OF QUINAPRILAT, PD  
113413, IN PATIENTS WITH VARYING DEGREES OF RENAL  
FUNCTION - PROTOCOL 906-255"

03-NOV-88 483 PR. 906-263-1

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DOC DATE	SER/SUPPL NO	TITLE
17-NOV-88	484	PR. 906-263-2
17-NOV-88	485	INFORMATION AMENDMENT
CONTENT: RR 764-01104 AUTHOR: KUGLER, A.R. ET AL DATE: 10-SEP-88 "DEVELOPMENT AND APPLICATION OF AN EQUILIBRIUM DIALYSIS METHOD TO DETERMINE QUINAPRIL AND QUINAPRILAT PROTEIN BINDING CHARACTERISTICS"		
17-NOV-88	486	PR. 906-262 CENTERS 3, 7, 10, 11, 19 AND 20
01-DEC-88	487	PR. 906-262 CENTERS 16 & 18/NEW SUB-INVESTIGATOR
CONTENT: PRS. 906-241-1 AND 906-241-1X WEINRAUCH, VIKTOR WOLFGANG, M.D.		
14-DEC-88	488	INFORMATION AMENDMENTS
CONTENT: REVISED PAGES RR 720-02338 COMPLETE REPORT DATE: 30-SEP-88 CROSS REFERENCE: SERIAL #424		
14-DEC-88	489	INFORMATION AMENDMENT
CONTENT: RR X-720-02394 AUTHOR: BERMAN, S.J. ET AL DATE: 18-NOV-88 "AN EIGHT-WEEK, PLACEBO-CONTROLLED, DOSE-RESPONSE MULTICENTER STUDY OF ORALLY ADMINISTERED QUINAPRIL HYDROCHLORIDE (CI-906) IN PATIENTS WITH MILD TO MODERATE HYPERTENSION (PROTOCOLS 906-238-1 TO 5, 906-238-7 TO 16, AND 906-238-18 TO 26)"		
21-DEC-88	490	PR. 906-262 CENTERS 9, 17, 21/NEW SUB-INVESTIGATOR
CONTENT: PR. 906-261-11 BURTON, ALBERT, M.D., CHB, MRCGP		
21-DEC-88	490	LETTER RE: PROTOCOL CANCELLATION - CONTINUED
CONTENT: LETTER TO: LIPICKY, RAYMOND J., M.D. PR. 906-261-9 RE: CANCELLATION OF PROTOCOL.		

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DOC DATE	SER/SUPPL NO	TITLE
21-DEC-88	491	PRS. 906-266-1 & 2
11-JAN-89	492	PR. 906-303-26
11-JAN-89	493	INFORMATION AMENDMENT
CONTENT:		
RR X-720-02392		
AUTHOR: EVANS, R. ET AL		
DATE: 11-NOV-88		
"INTERIM SUMMARY REPORT OF THE OPEN-LABEL PHASE OF FOUR MULTICENTER, DOUBLE-BLIND, PLACEBO- CONTROLLED STUDIES TO DETERMINE THE EFFICACY AND SAFETY OF ORALLY ADMINISTERED QUINAPRIL HYDROCHLORIDE (CI-906) IN PATIENTS WITH ESSENTIAL HYPERTENSION"		
30-JAN-89	494	PRS. 906-306-0, 307-0, 308-0, 314-0, 315-0
30-JAN-89	495	PR. 906-262-13/PROTOCOL AMENDMENTS/ADDENDUM
CONTENT:		
ADDENDUM NO. 1		
PR. 906-109		
ADDENDUM NO. 1		
PR. 906-171		
DATE: 2-APR-87		
ADDENDUM NO. 1		
PR. 906-252-1		
AMENDMENT NO. 1		
PR. 906-262-3		
DATE: 3-JAN-89		
AMENDMENT NO. 1		
PR. 906-295		
DATE: 7-DEC-88		
30-JAN-89	495	PROTOCOL AMENDMENTS/ADDENDUM - CONTINUED
CONTENT:		
AMENDMENT NO. 8		
PR. 906-66		
30-JAN-89	496	INFORMATION AMENDMENT
CONTENT:		
RR 724-00085		
AUTHOR: BERGHOFF, W. ET AL		
DATE: 8-DEC-88		
"REPORT OF A RANDOMIZED, DOUBLE-BLIND, PLACEBO- CONTROLLED TOLERANCE AND PHARMACOKINETIC STUDY OF SINGLE AND MULTIPLE ORAL DOSES OF QUINAPRIL HYDROCHLORIDE (CI-906) IN NORMAL SUBJECTS		



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08-FEB-89 497 PR. 906-303 CENTERS 1 THRU 17, 906-268-2, 906-277-0, 906-280

15-FEB-89 498 PR. 906-260 CENTERS 1 AND 2

CONTENT:

PR. 906-260-1 (JOSE A. YULDE, MD)  
906-260-2 (MARCELITO DURANTE, MD)

08-MAR-89 499 PRS. 906-243-0, 279-0, 296-0, 262-22, 303-18, 303-24, 303-25

08-MAR-89 499 PROTOCOL AMENDMENT/LETTER RE: PR. CANCELLATION - CONTINUED  
CONTENT:

AMENDMENT NO. 1  
PR. 906-303  
DATE: 21-DEC-88  
STATES THAT CPK SHOULD BE INCLUDED IN ALL FULL LAB  
LABORATORY DETERMINATIONS (SCREENING, V1 AND V2),  
ALSO, DOUBLING THE MEDICATION DOSE AT THE END OF  
THE WEEK 4.

PR. 906-132  
RE: CANCELLATION OF PROTOCOL.

15-MAR-89 500 PR. 906-268-3, 303 CENTERS 20,21,22,23,28/PROTOCOL AMENDMENT  
CONTENT:

AMENDMENT NO. 1  
PR. 906-303  
CORRECTION - AMENDMENT ONLY PERTAINS TO CENTERS  
NO. 1 THRU 19.  
CROSS REFERENCE: SERIAL #499

06-APR-89 501 PR. 906-319-0/NEW SUB-INVESTIGATOR

CONTENT:

PR. 906-262-19  
PALUMBO, REMIGIO, M.D.

06-APR-89 502 PR. 906-303 CENTERS 27 AND 31

08-MAY-89 503 PRS. 906-268-4 & 906-328-0

08-MAY-89 504 INFORMATION AMENDMENT  
CONTENT:

RR 764-01106  
AUTHOR: KUGLER, A.R. ET AL  
DATE: 27-MAR-89  
"IN VITRO QUINAPRIL METABOLISM IN RAT, DOG, MONKEY  
AND HUMAN LIVER PREPARATIONS"

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31-MAY-89 505 PRS. 906-333 CENTERS 1,10,11 AND 906-272-0/PR. AMENDMENT  
CONTENT:

AMENDMENT NO. 1  
PR. 906-282  
DATE: 24-AUG-88  
CHANGES THE FOLLOWING:  
1) SECTION IV CE, SUPINE BLOOD PRESSURE.  
2) SECTION V E4, SUPINE HEART RATE.  
3) SECTION VI B, BODY MASS INDEX > 30 KG/M2 OR  
<30 KG/M2.  
4) APPENDIX 3, CLINICAL LABORATORY DETERMINATION  
AND ECG WILL BE PERFORMED AT SCREENING (Q.V.  
SECTION V A) AND AT THE END OF BASELINE.

07-JUN-89 506 ANNUAL REPORT  
CONTENT:  
CUTOFF DATE: 8-MAY-89

07-JUN-89 507 PR. 906-304-0

07-JUN-89 508 INFORMATION AMENDMENT  
CONTENT:  
RR 745-01350  
AUTHOR: ULLOA, H.M. ET AL  
DATE: 9-MAY-89  
"DERMAL SENSITIZATION STUDY OF CI-906 (QUINAPRIL)  
IN GUINEA PIGS (MAXIMIZATION TEST)"

RR 745-01350  
AUTHOR: DETHLOFF, L.A. ET AL  
DATE: 10-MAY-89  
"THE EFFECTS OF CI-906 (QUINAPRIL) ON RENAL  
FUNCTION ON RENAL HEMODYNAMICS IN RATS"

RR 745-01384  
AUTHOR: MACDONALD, J.R. ET AL  
DATE: 9-MAY-89  
"EFFECTS OF CI-906 ADMINISTERED ORALLY FOR FOUR  
WEEKS ON RENAL FUNCTIONAL PARAMETERS IN MALE  
RATS"

07-JUN-89 508 INFORMATION AMENDMENT - CONTINUED  
CONTENT:

RR 745-01408  
AUTHOR: HENCK, J.W.  
DATE: 12-MAY-89  
"TWO-WEEK ORAL TOXICITY STUDY OF CI-906 IN FEMALE  
RABBITS"

RR 745-01412  
AUTHOR: PETRERE, J.A. ET AL  
DATE: 9-MAY-89  
"MODIFIED PENINATAL-POSTNATAL STUDY IN RATS WITH  
CI-906"

RR 745-01421

AUTHOR: KROPKO, M.L.

DATE: 9-MAY-89

"IN VITRO CHROMOSOMAL ABERRATION ASSAY OF CI-906  
IN V79 CHINESE HAMSTER LUNG CELLS"

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DOC DATE	SER/SUPPL NO	TITLE
07-JUN-89	508	INFORMATION AMENDMENT - CONTINUED
CONTENT:		RR 745-01430 AUTHOR: SUSICK, R.L. ET AL DATE: 9-MAY-89 "RENAL FUNCTION AND HEMODYNAMICS IN DOGS AFTER THIRTEEN-WEEK ORAL ADMINISTRATION OF CI-906"
		RR 745-01450 AUTHOR: GOUGH, A.W. ET AL DATE: 8-MAY-89 "HISTOPATHOLOGIC REVIEW OF KIDNEYS FROM RODENT CHRONIC TOXICITY STUDIES AND TUMOR BIOASSAYS WITH CI-906"
14-JUN-89	509	PR. 906-333 CENTERS 2, 4 AND 5/NEW PRINCIPLE INVESTIGATOR
CONTENT:		PR. 906-204-0 SAVRAN, STEPHEN, M.D.
22-JUN-89		MEMO RE: DISCUSSION WITH FDA
CONTENT:		RE: DISCUSSION ON 15-JUN-89 AFTER MEETING: 1) NDAS ON ACE INHIBITORS WOULD NOT BE BROUGHT BEFORE THE ADVISORY COMMITTEE 2) DEVELOPMENT ON ACE INHIBITORS/CALSIUM CHANNEL BLOCKER COMBINATION COULD BE APPROVED, BUT DEVELOPMENT MAY BE TECHNICALLY DIFFICULT.
22-JUN-89	510	PR. 906-309-0
29-JUN-89	511	PRS. 906-333 CENTERS 3, 6, 7 AND 906-33X CENTERS 3 AND 7
13-JUL-89	512	PRS. 906-330-0, 906-333 AND 333X CENTERS 9 & 12
27-JUL-89	513	PRS. 906-331-0/327-2,7,9,10/333 & 333X-2,9,10/263-4/273-1,2
27-JUL-89	514	INFORMATION AMENDMENT
CONTENT:		RR 740-02642 AUTHOR: TAYLOR, D.G. DATE: 23-JUN-89 "THE EFFECTS OF QUINAPIRL (Q) ON SYSTEMIC AND REGIONAL HEMODYNAMICS AND CARDIAC MASS IN WISTAR- KYOTO (WKY) AND SPONTANEOUSLY HYPERTENSIVE (SHR) RATS"

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DOC DATE	SER/SUPPL NO	TITLE
03-AUG-89	515	NEW SUB-INVESTIGATOR
CONTENT: PR. 906-262-22 CAVERO, PATRICIA, M.D.		
03-AUG-89	515	PRS. 906-327 & 327X CENTERS 5 AND 6
17-AUG-89	516	PRS. 906-327 & 327X CENTERS 1 AND 11/PR. 906-327-4
24-AUG-89	517	PR. 906-303-30
14-SEP-89	518	PRS. 906-335-0, 906-336-0, 906-327 & 327X-8
14-SEP-89	518	NEW SUB-INVESTIGATOR/PROTOCOL AMENDMENT
CONTENT: PR. 906-333-6 DRUEGER, DAVID, M.D. NAWAZ, DILSHER, M.D.  AMENDMENT NO. 1 PR. 906-304-0 THE DOSE OF DIURETIC MAY BE ADJUSTED IN RESPONSE TO PATIENT SYMPTOMS. HOWEVER, THE DOSE OF DIURETIC MUST BE STABILIZED AND CONSISTENT.		
14-SEP-89	519	INFORMATION AMENDMENT
CONTENT: RR 4301-00047 AUTHORS: BABOVIC-ALT, R. WIDMER, W. DATE: 4-AUG-89 "RANDOMIZED, SINGLE-BLIND Crossover STUDY COMPARING THE EFFICACY AND SAFETY OF ORALLY ADMINISTERED QUINAPRIL HYDROCHLORIDE (CI-906) WITH DIGOXIN ADDED TO HYDROCHLOROTHIAZIDE THERAPY IN PATIENTS WITH CONGESTIVE HEART FAILURE NYHA II (CT 891-002)"  RR 4301-00051 AUTHORS: BALKOVIC-ALT, R. LILIENTHAL, J. DATE: 4-AUG-89 "REPORT OF A ONE-YEAR, OPEN-LABEL, MULTICENTER STUDY FOLLOWING A 12-WEEK, DOUBLE-BLIND, PLACEBO- CONTROLLED STUDY TO DETERMINE EFFICACY AND SAFETY OF ORALLY ADMINISTERED CI-906 (QUINAPRIL (CT 891-140)"		

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14-SEP-89 519 INFORMATION AMENDMENT - CONTINUED  
CONTENT:

RR 740-02586  
AUTHORS: CASAD, B.  
KEISER, J.  
DATE: 28-AUG-89  
"A MULTIPLE-DOSE STUDY TO ASSESS THE FUNCTIONAL  
INTERACTION OF QUINAPRIL (CI-906) AND  
HYDROCHLOROTHIAZIDE (CI-570) IN SALINE-LOADED  
NORMOTENSIVE RATS"

28-SEP-89 520 PRS. 906-327 & 327X CENTER 3

28-SEP-89 521 INFORMATION AMENDMENT  
CONTENT:

RR 740-02536  
AUTHOR: RAPUNDALO, S. ET AL  
DATE: 31-AUG-89  
"COMPARATIVE EFFECTS OF QUINAPRIL AND QUINAPRILAT  
ON VARIOUS PROTEINASES"

RR 740-02694  
AUTHOR: CASAD, B. ET AL  
DATE: 1-SEP-89  
"A MULTIPLE-DOSE STUDY TO ASSESS THE FUNCTIONAL  
INTERACTION OF QUINAPRIL (CI-906) AND  
HYDROCHLOROTHIAZIDE (CI-570) IN SALINE-LOADED  
SPONTANEOUSLY HYPERTENSIVE RATS"

12-OCT-89 522 PR. 906-321-0

26-OCT-89 523 PR. 906-334 CENTERS 1, 2, 3, 4, 5 AND 6  
CONTENT:  
The coinvestigators shall conduct this protocol at  
their respective centers.

31-OCT-89 524 LETTER RE: CONFIRMATION OF MEETING  
CONTENT:  
LETTER TO: LIPICKY, RAYMOND J., M.D.  
RE: CONFIRMATION OF PRE-NDA MEETING ON 28-NOV-89  
AT 10 AM.  
ATTACHED DRAFT REPORT (RR 720-02593) FOR  
PR. 906-241.

14-NOV-89 MEMO RE: VERBAL CONFIRMATION  
CONTENT:  
TELEPHONE CONVERSATION WITH KATHLEEN BONGIOVANNI.  
re: Confirmation that Dr. Temple would be at the  
18-NOV-89 PRE-NDA MEETING.

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14-NOV-89 525 PRS. 906-215, 317 & 341-0/NEW SUB-INVESTIGATOR  
CONTENT:  
PR. 906-224  
NORTHRIDGE, DAVID, MRCP

14-NOV-89 525 PROTOCOL ADDENDUMS/AMENDMENT  
CONTENT:  
ADDENDUM NO. 1  
PR. 906-215  
  
ADDENDUM NO. 2  
PR. 906-224  
  
AMENDMENT NO. 3  
PR. 906-224  
DATE: 7-DEC-88

01-DEC-89 526 SAFETY REPORT  
CONTENT:  
PATIENT NO.: 8 (LL)  
PR. 906-331-0  
AE: SUSPECTED HEPATITIS.  
DEATH WAS CONTRIBUTED TO PEPTIC ULCER DISEASE.  
WAS SUBMITTED AS A "CLINICAL INFORMATION  
AMENDMENT."  
AE 001-0906-890035-00

08-DEC-89 527 MINUTES OF FDA MEETING  
CONTENT:  
28-NOV-89  
FDA PRE-NDA MEETING ON CI-955.

11-DEC-89 MEMO RE: VERBAL REQUEST FOR INFORMATION  
CONTENT:  
TELEPHONE CONVERSATION WITH KATHLEEN BONGIOVANNI,  
FDA.  
RE: CLINICAL REPORT SENT 1-DEC-89 (REPORT OF  
HEPATITIS):  
1) REQUESTED RESULTS OF MICROSCOPIC EXAMINATION.  
2) QUESTIONED WHY SUBMISSION WAS SENT UNDER  
"CLINICAL INFORMATION".

13-DEC-89 MEMO RE: VERBAL REQUEST FOR INFORMATION  
CONTENT:  
TELEPHONE CONVERSATION FROM DR. CHERYL GRAHAM, FDA  
RE: CLINICAL REPORT SENT 1-DEC-89 (REPORT OF  
HEPATITIS).  
ASSESSMENT SHOULD BE SENT TO ALL INVESTIGATORS.

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20-DEC-89 MEMO RE: VERBAL REQUEST FOR INFORMATION  
CONTENT: TELEPHONE CONVERSATION STATING DR. B. FREIDMAN  
IS NOW OUR QUINAPRIL IND MEDICAL REVIEWER.

20-DEC-89 528 LETTER RE: SUBMISSION CORRECTION  
CONTENT: LETTER TO: LIPICKY, RAYMOND J., M.D.  
RE: SERIAL #526 CATEGORY.  
RECATEGORYIZE 1-DEC-89 LETTER FROM "CLINICAL  
INFORMATION AMENDMENT" TO "IND SAFETY REPORT".

20-DEC-89 529 PR. 906-311 CENTERS 1, 3, 5, 6 AND 8

02-JAN-90 MEMO RE: VERBAL REQUEST FOR INFORMATION  
CONTENT: TELEPHONE CONVERSATION WITH DR. FRIEDMAN.  
RE: QUINAPRIL IND AND NDA.  
1) DR. JOHN VILLUAME HAS LEFT PARKE-DAVIS.  
2) CONFIRMING HIS APPOINTMENT AS MEDICAL REVIEWER.  
3) REVIEW OF THE PRE-NDA MEETING FOR CI-955.

03-JAN-90 530 SAFETY REPORT  
CONTENT: PATIENT NO.: 8 (LL)  
PR. 906-331-0  
AE: SUSPECTED HEPATITIS.  
POSSIBLE DRUG RELATED.  
FOLLOW-UP REPORT - SERIAL #526  
AE 001-0906-890035-00

05-JAN-90 MEMO RE: VERBAL REQUEST FOR INFORMATION  
CONTENT: TELEPHONE CALL FROM KATHLEEN BONGIOVANNI, FDA.  
RE: 10-DAY SAFETY REPORT FOLLOW-UP (SERIAL #526)..  
DR. FRIEDMAN RECEIVED FAX, PLACE HOLD ON  
INVESTIGATOR'S LETTER UNTIL FDA REVIEW IS  
COMPLETED.

11-JAN-90 531 PR. 906-312 CENTERS 0,2,4,5,6,7,14 & 15/NEW PRIMARY INVEST.  
CONTENT: PR. 906-262-11  
O'ROURKE, ROBERT, M.D.



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17-JAN-90 532 SAFETY REPORT  
CONTENT:

PATIENT NO.: 8 (LL)  
PR. 906-331-0  
AE: SUSPECTED HEPATITIS.  
POSSIBLE DRUG RELATED.  
FOLLOW-UP REPORT - SERIAL #526  
REVISED INVESTIGATOR'S LETTER.  
AE 001-0906-890035-00

01-FEB-90 533 PROTOCOL AMENDMENT  
CONTENT:

AMENDMENT NO. 1  
PR. 906-340  
PROVIDES FOR ADDITIONAL REQUIREMENTS SPECIFIED BY  
THE TWO GERMAN IRBS FOR PATIENT SCREENING AND  
PLACEBO BASELINE.

01-FEB-90 534 INFORMATION AMENDMENT  
CONTENT:

RR 720-02398  
AUTHOR: CANTER, D.A. ET AL  
DATE: 11-OCT-89  
"A 12-WEEK, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY  
TO DETERMINE THE EFFICACY AND SAFETY OF ORALLY  
ADMINISTERED QUINAPRIL HYDROCHLORIDE (CI-906)  
IN PATIENTS WITH CONGESTIVE HEART FAILURE  
(PROTOCOLS 906-63 TO -69, -72 TO -75, -77 TO -79,  
-204, -205, -216, -218, -219, -233-2, AND  
-233-5)"

RR 720-025821)"  
AUTHOR: CANTER, D.A. ET AL  
DATE: 22-DEC-89  
"A 14-WEEK, OPTIONAL-TITRATION, MULTICENTER,  
DOUBLE-BLIND STUDY TO COMPARE THE EFFICACY AND  
SAFETY OF ORALLY ADMINISTERED QUINAPRIL  
HYDROCHLORIDE (CI-906) WITH CAPTOPRIL IN PATIENTS  
WITH MILD TO MODERATE ESSENTIAL HYPERTENSION  
(PROTOCOL 906-100, -102 TO -106, -109 TO -111)"

01-FEB-90 534 INFORMATION AMENDMENT - CONTINUED  
CONTENT:

RR 764-01367  
AUTHOR: BMMERT, J.A. ET AL  
DATE: 30-NOV-89  
"A BIOAVAILABILITY STUDY OF QUINAPRIL HCL 20-MG  
COMMERCIAL TABLETS, 20-MG INVESTIGATIONAL  
CAPSULES, AND A 20-MG ORAL SOLUTION IN HEALTHY  
VOLUNTEERS: PROTOCOL 906-328"

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DOC DATE	SER/SUPPL NO	TITLE
08-FEB-90	535	LETTER RE: REQUEST FOR REVIEW AND COMMENTS
CONTENT:		LETTER TO: LIPICKY, RAYMOND J., M.D. RE: PR. 906-276
08-FEB-90	536	PR. 906-313-0
15-FEB-90	537	LETTER TO: PROTOCOL CANCELLATION
CONTENT:		LETTER TO: LIPICKY, RAYMOND J., M.D. PR 906-262-18 RE: CANCELLATION OF PROTOCOL
15-FEB-90	537	PRS. 906-343 & 343X-0, PR. 906-311 CENTERS 4, 7, 10 & 11
22-FEB-90	538	INFORMATION AMENDMENT/IB UPDATE
CONTENT:		RR 764-01432 AUTHOR: OLSON, S.C. ET AL DATE: 22-JAN-90 "EFFECTIVE ACCUMULATION HALF-LIFE FOR QUINAPRILAT FOLLOWING QUINAPRIL DOSING: PROTOCOL 906-305-0"  DATE: 9-MAY-89 RR X-720-02572 AUTHORS: DAWKIN, R. PURCELL, T.J. SUPERSEDES RR X-720-02277
01-MAR-90	539	PR. 906-340 CENTERS 5 AND 7/PROTOCOL AMENDMENT
CONTENT:		AMENDMENT NO. 1 PR. 906-340-7 DATE: 8-SEP-89 PROVIDES FOR ADDITIONAL REQUIREMENTS SPECIFIED BY THE IRB.
01-MAR-90	540	PR. 906-340 CENTERS 21 & 22, PR. 906-346-0
05-MAR-90		MEMO RE: VERBAL REQUEST FOR INFORMATION
CONTENT:		TELEPHONE CONVERSATION OF 2-MAY-90 & 5-MAY-90. RE: PROPOSED CHF STUDY 906-276. 1) INCONSISTENCEIS IN INFORMATION ON PAGES 5, 11 AND 19. (2-MAY-90) 2) REQUESTED INPUT ON THE USE OF EXERCISE TOLERANCE. (2-MAY-90) 3) REQUESTED SAMPLE CASE REPORT FORM. (5-MAY-90) 4) EXCERCISE TOLERANCE IS A SUITABLE PRIMARY EFFICACY PARAMETER. (5-MAY-90) 5) WANT TO REVIEW GUIDELINES ON CHF. (5-MAY-90)

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DOC DATE	SER/SUPPL NO	TITLE
14-MAR-90	541	LETTER RE: REQUEST FOR REVIEW AND COMMENTS
CONTENT:		LETTER TO: LIPICKY, RAYMOND J., M.D. RE: PROTOCOL 906-239. CROSSFILE IND 34,487 (CI-955)
22-MAR-90	542	PRS. 906-344-0 & 902-348-0/NEW SUB-INVESTIGATOR
CONTENT:		PR. 906-268-4 GUEZI, BOUALEM, M.D.
29-MAR-90	543	PR. 906-340 CENTERS 14, 25, 26 AND 28
19-APR-90	544	PRS. 906-311-2 & 12/906-312-12/906-340 CNTS 1,2,16,17,23,24
26-APR-90	545	PRS. 906-276-1,2,3,6,9,12,14,22/310-13,30,39,42,43,44/345-13
01-MAY-90		MEMO RE: REQUEST FDA MEETING
CONTENT:		MEMO RE: TELEPHONE CONVERSATION ON 23-APR-90 REGARDING A FDA VISIT.
03-MAY-90	546	PRS. 906-376 CENTERS 8, 16/906-355 CENTERS 1 THRU 10
10-MAY-90		LETTER FROM FDA RE: MINUTES OF FDA MEETING
CONTENT:		LETTER FROM: MORGENSTER, NATALIA A. DATE: 28-NOV-89 FDA MINUTES
14-MAY-90	547	PRS. 906-345 CENTERS 31-34, 37,38/906-276 CENTERS 3,7,13
15-MAY-90		MINUTES OF FDA MEETING
CONTENT:		DATE: 28-NOV-89 FDA MEETING RE: PRE-NDA MEETING FOR QUINAPRIL/HCTZ COMBINATION PRODUCT
18-MAY-90	548	LETTER RE: INFORMATION
CONTENT:		LETTER TO: LIPICKY, RAYMOND J., M.D. RE: GENERAL CORRESPONDENCE

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DOC DATE	SER/SUPPL NO	TITLE
21-MAY-90	549	PRS. 906-276 CENTERS 5,11,25/906-340 CENTERS 10,11,12,13,27
21-MAY-90	549	PR. 906-345 CENTERS 14,35,36,40,41,45,46,47 AND 48
30-MAY-90	550	PR. 906-276-10
06-JUN-90	551	PR. 906-276-20
18-JUN-90	552	NEW PRINCIPLE INVESTIGATOR/AMENDMENT
CONTENT:		
PR 906-276/906-276X-15 COLFER, HARRY, M.D.		
PR 906-276/906-276X-19 BAIRD, MICHAEL G., M.D.		
AMENDMENT NO. 1 PR 906-276 AND 906-276X DATE: 25-MAY-90 CHANGES ON PAGES 8, 10, 12, 13, 16 AND 19 DATE: 15-MAY-90 CHANGES ON PAGES 2 AND 3		
18-JUN-90	553	INFORMATION AMENDMENT
CONTENT:		
RR 4301-00064 AUTHORS: SCHLUTTENHOFER, H ET AL DATE: 28-FEB-90 "A SINGLE-BLIND STUDY TO EVALUATE TOLERANCE AND EFFICACY OF A WEEK OF CONCOMITANT THERAPY WITH DILTIAZEM AND QUINAPRIL FOLLOWING A WEEK OF MONOTHERAPY WITH QUINAPRIL IN PATIENTS WITH HYPERTENSION (PROTOCOL 906-252)"		
RR 720-02735 AUTHORS: CANTER, D ET AL DATE: 01-MAR-90 "AN 18-WEEK, DOUBLE-BLIND, OPTIONAL-TITRATION, MULTICENTER STUDY TO COMPARE THE EFFICACY AND SAFETY OF ORALLY ADMINISTERED QUINAPRIL HYDROCHLORIDE (CI-906) WITH CAPTOPRIL AND PLACEBO IN PATIENTS WITH CHRONIC CONGESTIVE HEART FAILURE (PROTOCOLS 906-226-01 TO -16, -18 TO -30, 32 TO -34)"		

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DOC DATE SER/SUPPL NO TITLE

18-JUN-90 553 INFORMATION AMENDMENT - CONTINUED  
CONTENT:

RR 720-02703  
AUTHORS: CANTER, D ET AL  
DATE: 05-MAR-90  
"A 12-WEEK, DOUBLE-BLIND CROSSOVER STUDY  
EVALUATING THE ANTIHYPERTENSIVE EFFECTS OF ONCE  
AND TWICE DOSE DAILY QUINAPRIL HYDROCHLORIDE  
(CI-906) ON 24-HOUR AMBULATORY BLOOD PRESSURE  
AND LEFT VENTRICULAR FUNCTION IN PATIENTS WITH  
ESSENTIAL HYPERTENSION (PROTOCOL 906-289-0,  
9-011-0)"

18-JUN-90 553 INFORMATION AMENDMENT - CONTINUED  
CONTENT:

RR 720-02705  
AUTHORS: CANTER, D ET AL  
DATE: 26-APR-90  
"SAFETY REPORT OF AN EIGHT-WEEK, SINGLE-CENTER,  
DOUBLE-BLIND STUDY OF THE EFFECTS OF FOUR DOSES  
OF QUINAPRIL HYDROCHLORIDE (CI-906) ON THE  
RENIN-ANGIOTENSIN-ALDOSTERONE-CATECHOLAMINE AXIS  
IN PATIENTS WITH HYPERTENSION (PROTOCOL  
906-213-0, 9-015-0)"

18-JUN-90 554 INFORMATION AMENDMENT  
CONTENT:

RR 760-00011  
AUTHOR: SCHRIER, D  
DATE: 16-FEB-90  
"THE EFFECTS OF QUINAPRIL, CAPTOPRIL, AND  
ENALAPRIL IN CARRAGEENAN FOOTPAD EDEMA (CFE),  
A RAT ACUTE MODEL OF INFLAMMATION"

RR 740-02796  
AUTHORS: RYAN, MJ ET AL  
DATE: 26-FEB-90  
"ANTIHYPERTENSIVE ACTIVITY OF QUINAPRIL GIVEN FOR  
14 DAYS TO CONSCIOUS SPONTANEOUSLY HYPERTENSIVE  
RATS"

18-JUN-90 554 INFORMATION AMENDMENT - CONTINUED  
CONTENT:

RR 740-02799  
AUTHORS: HALEEN, SJ ET AL  
DATE: 05-MAR-90  
"THE EFFECTS OF QUINAPRIL ON THE TEMPORAL  
PROGRESSION OF LEFT VENTRICULAR FAILURE IN THE  
CARDIOMYOPATHIC HAMSTER"

RR 4192-00422  
AUTHORS: NEUB, M ET AL  
DATE: 23-APR-90  
"DOSE-PROPORTIONALITY AND SYSTEMIC EXPOSURE OF  
QUINAPRILAT IN MICE AND RATS FOLLOWING MULTIPLE  
DOSE ADMINISTRATION OF QUINAPRIL (PROTOCOL 906-289-0,  
9-011-0)"

90-001 AND 90-002)"

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25-JUN-90 555 NEW PRINCIPAL INVESTIGATORS

CONTENT:

906-276-17  
WALTERS, DAVID, M.D.

906-276-23  
PANTAZOPOULOS, J, M.D.

906-276-24  
SINGH, STEVEN, M.D.

906-345-01  
LEARY, WP, PROF.

906-345-02  
MYBURGH, DP, M.D.

906-345-03  
SARELI, P, M.D.

25-JUN-90 555 NEW PRINCIPAL INVESTIGATORS - CONTINUED

CONTENT:

906-345-11  
HENDRIKA, J, M.D.

906-345-17  
BUONINCONTI, RAFFAELLO, PROF.

11-JUL-90 FDA CONTACT MEMO

CONTENT:

MEMO RE: CI-906  
CONTACT PERSON: FRIEDMAN, DR.  
TELEPHONE CONVERSATION RE:  
REQUEST FOR CLARIFICATION OF CAUSES OF DEATH  
IN STUDY 906-226.

12-JUL-90 FDA CONTACT MEMO

CONTENT:

MEMO RE: CI-906  
FDA CONTACT PERSON: FRIEDMAN, BASIL, DR.  
TELEPHONE CONVERSATION RE:  
FOLLOW-UP TO REQUEST FOR CLARIFICATION OF  
COURSES OF DEATH - STUDY 906-226.

12-JUL-90 556 PROTOCOL AMENDMENT - NEW PRINCIPLE / SUB INVESTIGATORS

CONTENT:

AMENDMENT NO. 1  
PR. 906-345-11  
DATE: 12-JUL-90  
AMENDMENT PERTAINS TO THIS SITE ONLY; PURPOSE IS  
TO SATISFY THE ETHICAL COMMITTEE REQUIREMENT THAT  
IF A PATIENT'S DIASTOLIC BLOOD PRESSURE RISES TO  
100 NNHG OR MORE DURING PLACEBO THE PATIENT WILL  
WITHDRAW.

PR. 906-345-12  
HOUTZAGERS, J.J.R., M.D.

PR. 906-345-18  
WESTER, ANNO

PR. 906-340-15  
ROSENQVIST, ULF



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12-JUL-90 556 AMENDMENT - NEW PRINCIPLE / SUB INVESTIGATORS - CONTINUED  
CONTENT:

PR. 906-340-19  
TASKINEN, ESKO

SUBINVESTIGATOR'S

PR. 906-311-10  
MCDAID, P. DR.

PR. 906-282  
STARK, SANDRA

12-JUL-90 557 INFORMATION AMENDMENT  
CONTENT:

RR 740-02797  
AUTHORS: PANEK, R.L. ET AL  
DATE: 13-JUN-90  
"ANTIHYPERTENSIVE RESPONSE TO QUINAPRIL: ROLE OF  
CIRCULATING AND TISSUE ANGIOTENSIN CONVERTING  
ENZYME (ACE) ACTIVITY"

12-JUL-90 558 INFORMATION AMENDMENT  
CONTENT:

RR 4301-00055  
AUTHORS: SCHLUTTENHOFER, H, ET AL  
DATE: 30-MAY-90  
"A SINGLE-BLIND PILOT TO EVALUATE TOLERANCE AND  
EFFICACY OF A WEEK OF CONCOMITANT THERAPY WITH  
QUINAPRIL AND DILTIAZEM FOLLOWING A WEEK OF  
MONOTHERAPY WITH DILTIAZEM IN INPATIENTS WITH  
HYPERTENSION (PROTOCOL 906-251)"

RR 764-01432  
AUTHORS: OLSON, S.C. ET AL  
DATE: 22-JAN-90  
"EFFECTIVE ACCUMULATION HALF-LIFE FOR QUINAPRILAT  
FOLLOWING QUINAPRIL DOSING: PROTOCOL 906-305-0"

12-JUL-90 558 INFORMATION AMENDMENT - CONTINUED  
CONTENT:

RR 764-01473  
AUTHORS: BMMERT, J.A. ET AL  
DATE: 11-APR-90  
"ABSOLUTE BIOAVAILABILITY AND PHARMACOKINETICS OF  
QUINAPRILAT IN HEALTHY VOLUNTEERS FOLLOWING  
SINGLE-DOSE ADMINISTRATION OF ORAL QUINAPRIL  
(CI-906) AND INTRAVENOUS QUINAPRILAT (CI-928):  
PROTOCOL 906-342"

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CI NUMBER= 906 APPL NUMBER= 20,336

DOC DATE	SER/SUPPL NO	TITLE
13-JUL-90		FDA CONTACT MEMO
CONTENT:		MEMO RE: CI-906/CI-955 CONTACT PERSON: WOLTERS, ROBERT, DR. MEETING RE: QUESTION ON PENDING QUINAPRIL NDA FUTURE Q/HCTZ NDA EA
19-JUL-90	559	PROTOCOL AMENDMENT - NEW PRINCIPLE INVESTIGATOR
CONTENT:		AMENDMENT NO. ONE PR. 906-349 THE ADDITION OF AN AUTOMATED BLOOD PRESSURE MONITOR RECORDING AT WEEK 12 OF THE DOUBLE-BLIND PERIOD.  PR. 906-349-07 BARRY, PAULL, M.D.  PR. 906-349-11 WOMBOLT, DUANE, G., M.D.  PR. 906-276-13 BAILEY, JOHN, M.D.
19-JUL-90	560	ANNUAL REPORT
CONTENT:		ISSUE DATE: 16-JUL-90
19-JUL-90	561	LETTER RE: REPLY TO FDA QUESTIONS OF 11-JUL-90
CONTENT:		LETTER TO: LIPICKY, RAYMOND, J., M.D. TELEPHONE CONVERSATION: REQUEST FOR ADDITIONAL INFORMATION ON PATIENTS WHO DIED DURING STUDY PROTOCOL 906-226
26-JUL-90	562	PROTOCOL AMENDMENTS - NEW INVESTIGATOR
CONTENT:		AMENDMENT NO. 1 PR. 906-340-15 TO ALLOW PROLONGED TREATMENT OF PATIENTS HAVING BENEFITFROM THE 906-340 STUDY.  AMENDMENT NO. 1 PR. 906-340-22 INTENSIFY BLOOD PRESSURE FOR PATIENTS WITH SEVERE HYPERTENSION DURING THE BASLINE PLACEBO PHASE AND TAKE THE LEVEL OF SYSTOLIC BLOOD PRESSURE INTO CONSIDERATION.  PR. 906-340-08 PUJADES, JUAN, OCON, M.D.  PR. 906-340-09 CONZALEZ, RAMON, DOMERO, M.D.

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DOC DATE	SER/SUPPL NO	TITLE
26-JUL-90	562	PROTOCOL AMENDMENT - NEW INVESTIGATOR - CONTINUED
CONTENT:		PR. 906-349-1 WEINER, GERALD, M., M.D.  PR. 906-349-5 MARBURY, THOMAS, C., M.D.  PR. 906-349-8 ROSENBAUM, ROBERT, M.D.
26-JUL-90	563	INFORMATION AMENDMENT
CONTENT:		RR 4301-00060 AUTHORS: EYSELL, J., ET AL DATE: 18-APR-90 "REPORT ON A TWELVE-WEEK, DOUBLE-BLIND, PARALLEL- GROUP, MULTICENTER STUDY TO DETERMINE THE EFFICACY AND SAFETY OF CI-906 (QUINAPRIL HYDROCHLORIDE) AND CAPTOPRIL, WHEN ORALLY ADMINISTERED IN ADDITION TO HYDROCHLOROTHIAZIDE TO PATIENTS WITH MODERATE TO SEVERE ESSENTIAL HYPERTENSION (WLI 9-030-0)"
27-JUL-90	564	SAFETY REPORT
CONTENT:		PATIENT NO.: NONE (VAT) FRANCE AE: ANAPHYLACTIC SHOCK AE 033-0906-900058-00
02-AUG-90	565	INFORMATION AMENDMENT
CONTENT:		RR MEMO 720-02809 AUTHORS: CANTER, D. ET AL DATE: 17-JUL-90 "AN INTERIM REPORT ON THE EFFICACY AND SAFETY OF QUINAPRIL IN PATIENTS WITH MILD TO MODERATE HYPERTENSION AND MODERATE TO SEVERE CONCOMITANT RENAL IMPAIRMENT (PROTOCOLS 906-263-1 THROUGH 906-263-4 AND 906-268-1, 906-268-2 AND 906-268-4)"
02-AUG-90	566	NEW INVESTIGATOR / PROTOCOL AMENDMENT
CONTENT:		PR 906-349-2 GOLDSTEIN, MARK, M.D.  PR 906-345-10 IKRAM, HAMID, M.D.  NEW SUBINVESTIGATORS PR 906-311 WILLIAMS, PETER, HOWARD, M.D. HAYMON, STEVEN, RICHARD, M.D.

SPECIAL AMENDMENT

PR. 906-349-2 (ONLY)

DATE: 15-JUN-90

PURPOSE IS TO DECREASE THE UPPER LIMIT OF THE  
ENTRY CRITERIA FOR DIASTOLIC BLOOD PRESSURE TO  
110 MM HG

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DOC DATE	SER/SUPPL NO	TITLE
09-AUG-90		FDA CONTACT MEMO
CONTENT:		MEMO RE: CI-906 CONTACT PERSON: FRIEDMAN, BASIL, DR. TELEPHONE CONVERSATION: CLARIFICATION OF INFORMATION IN RR 4301-00060
09-AUG-90	567	NEW PRINCIPLE INVESTIGATOR
CONTENT:		PR. 906-345-21 QUOIDBACH, ALBERT, M.D.  PR. 906-345-24 LAVILLE, MAURICE, M.D.  PR. 906-349-06 NEDELMAN, PHILIP, M.D.  PR. 906-349-09 SILBAUGH, BARRY, M.D.
13-AUG-90	568	RESPONSE TO FDA REQUEST FOR INFORMATION
CONTENT:		LETTER TO: LIPICKY, RAYMOND, J., M.D. CI-906 RE: RESPONSE TO TELEPHONE CONVERSATION FROM FRIEDMAN, BASIL, DR. ON 09-AUG-90; TWO QUESTIONS CONCERNING STUDY REPORT ON PROTOCOL 9-030-0.
16-AUG-90	569	NEW PRINCIPLE INVESTIGATOR
CONTENT:		PR. 906-349-03 HORWITZ, LAWRENCE, M.D.  PR-906-349-04 IDSV00G, PETER, M.D.  PR. 906-349-12 YELLEN, LAURENCE, G., M.D.  PR-906-276-21 REDDY, C.V., M.D.
21-AUG-90		FDA CONTACT MEMO
CONTENT:		MEMO RE: CI-906 FDA CONTAC PERSON: BONGIOVANNI, K. MEETING AT FDA RE: STATUS OF PENDING QUINAPRIL NDA.

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DOC DATE	SER/SUPPL NO	TITLE
23-AUG-90	570	PROTOCOL AMENDMENT / NEW PRINCIPLE INVESTIGATOR
CONTENT:		AMENDMENT NO. 1 PR.906-345 EXCLUDES PATIENTS WITH BRADYCARDIA (HEART RATE < 55); ALLOWS INCLUSION OF PATIENTS WITH HEART RATE > 50. THIS CHANGE WAS REQUESTED BY THE ETHICAL COMMITTEE IN FINLAND.
30-AUG-90	571	PR. 423-906-350/NEW SUB-INVESTIGATORS
CONTENT:		PR. 906-282 STARK, SISTER SANDRA  PR. 906-311-10 MCCAID, P., M.D.
30-AUG-90	572	LETTER RE: FOLLOW UP TO SAFETY REPORT
CONTENT:		LETTER TO: LIPICKY, RAYMOND, J., M.D. RE: FOLLOW UP TO A WRITTEN SAFETY REPORT ( SERIAL NO. 564, JULY 27, 1990) .
06-SEP-90	573	INFORMATION AMENDMENT
CONTENT:		RR 720-02817 AUTHORS: KIMMEL, K.A., ET AL DATE: 23-AUG-90 "INITIAL REPORT OF THE PRIMARY EFFICACY ANALYSIS OF A 24-WEEK, DOUBLE-BLIND, PLACEBO-CONTROLLED, DOSE-TITRATION, MULTICENTER, THREE-WAY CROSSOVER STUDY COMPARING THE EFFICACY AND SAFETY OF QUINAPRIL HYDROCHLORIDE (CI-906) QD AND BID IN THE TREATMENT OF PATIENTS WITH CONGESTIVE HEART FAILURE (PROTOCOLS 906-215, -224, AND -295)"
06-SEP-90	574	NEW PRINCIPLE INVESTIGATOR
CONTENT:		PR 906-345-19 MIEVIS, ERIC, M.D.  PR 906-349-10 WHELTON, ANDREW, M.D.
13-SEP-90	575	NEW PRINCIPLE INVESTIGATOR / PROTOCOL AMENDMENT
CONTENT:		PR. 906-276-27 ZELLNER, STEPHEN, R., M.D.  PR. 906-317 SAAL, JEAN-PIERRE, M.D. WILL WORK UNDER CASTAIGNE, ALAIN, M.D.

PR. 906-346-0

DATE: 26-FEB-90

THIS AMENDMENT ASSURES THAT THE NEWEST PUERTO RICO  
FORMULATIONS ARE USED IN THIS STUDY.

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18-SEP-90 FDA CONTACT MEMO  
CONTENT:

MEMO RE: CI-906  
FDA CONTACT PERSON: BONGIOVANNI, K.  
TELEPHONE CONVERSATION RE:  
QUESTION ON RR 4301-00060 IN SERIAL NO. 563

SURVEY ON PEDIATRICS STUDIES FOR NDA PRODUCTS  
IS UNDER REVIEW; SHE IS FAXING A COPY OF THE  
SURVEY AND WOULD LIKE US TO RESPOND IN A LETTER  
TO OUR NDA.

27-SEP-90 576 NEW PROTOCOL / NEW SUB-INVESTIGATOR'S  
CONTENT:

PR. 906-352 CENTERS 1 AND 2  
INTERNATIONAL STUDY NUMBER  
421-906-014 CENTERS 1 AND 2

PR. 906-350-0  
INTERNATIONAL STUDY NUMBER  
906-350-410

NEW SUB-INVESTIGATOR'S  
906-276-22  
ABELL, MARY, M.D.  
FARUQ, DALIRA, M.D.

11-OCT-90 577 PR. 906-357 CENTERS 1,2,3,4,5,6,7,/906-276-29/NEW SUB-INVEST  
CONTENT:  
PR. 906-276-3  
CARBERRY, PETER A., M.D.

22-OCT-90 578 PR. 906-276-28/NEW PRINCIPLE INVESTIGATOR  
CONTENT:  
PR. 906-311-9  
AMIN, M.S., DR.

31-OCT-90 579 PR. 906-351-0 (906-001-455)/PROTOCOL AMENDMENT  
CONTENT:  
AMENDMENT NO. 1  
PR. 906-351-0  
CLARIFIES THE INCLUSION AND EXCLUSION CRITERIA.

08-NOV-90 580 PR. 906-345X-3



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DOC DATE	SER/SUPPL NO	TITLE
16-NOV-90	581	PR. 906-345-20/PR. 906-325-0
26-NOV-90	582	PR. 906-371-0
03-DEC-90	583	PR. 906-410002-0/906-369-0/906-410003-0
03-DEC-90	584	NEW SUB-INVESTIGATOR
CONTENT: PR. 906-349-4 MCAWEENEY, WILLIAM J., M.D.		
11-DEC-90	585	PROTOCOL AMENDMENT
CONTENT: AMENDMENT NO. 1 PR. 906-340-15 DATE: 02-JUL-90 ALLOWS FOR THE PROLONGED TREATMENT FOR RESPONDERS OF THIS PROTOCOL.		
21-DEC-90	586	SAFETY REPORT
CONTENT: PATIENT NO.: NONE (WB) PR. 432-906-600-2045 AE: EXPERIENCED A MYOCARDIAL INFARCTION POSSIBLY DRUG RELATED AE 049-0906-9000005-00		
31-DEC-90	587	PR. 906-318 CENTERS 1-7/ 906-430012/ 906-276-25
24-JAN-91		FDA CONTACT MEMO
CONTENT: MEMO RE: QUESTIONS ON CHF PROTOCOL (IND SER #587) CONTACT PERSON: SOMANI, PETER, DR. TELEPHONE CALL FROM FDA RE: QUESTIONS REGARDING 906-318. 1: ON P.4, PLEASE CLARIFY TITRATED DOSAGE. 2: PLEASE PROVIDE A RATIONALE FOR DOSE SELECTION (IF 50 MG TID). 3: PROVIDE INFORMATION REGARDING OXYGEN AND CARBON DIOXIDE PARTIAL PRESSURE & AIR FLOW. 4: PROVIDE TREATMILL TIME STATGE.		
24-JAN-91		FDA CONTACT MEMO
CONTENT: MEMO RE: REQUEST TO OPEN SEPARATE IND FOR CHF INDICATION FOR QUINAPRIL CONTACT PERSON: BONGIOVANNI, KATHLEEN, CSO TELEPHONE CALL FROM FDA RE: REQUEST A NEW IND FOR THE CHF INDICATION FOR QUINAPIRL.		

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DOC DATE SER/SUPPL NO TITLE

25-JAN-91 588 PR. 906-430008-0

30-JAN-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: PROVIDED INFORMATION REGARDING CHF  
INDICATION FILING  
CONTACT PERSON: BONGIOVANNI, KATHLEEN, CSO  
TELEPHONE CALL FROM FDA RE: DR. GRAHAM PROVIDED  
AND REQUESTED THE FOLLOWING INFORMATION:  
1) NO NEW IND NEEDED FOR THE CHF INDICATION DUE  
TO THE LATE STAGE OF DEVELOPMENT.  
2) PLEASE PROVIDE OVERVIEW OF THE PROPOSED  
SUPPLEMENTAL NDA FOR CHF.  
3) PROVIDE A LIST OF STUDIES SEPARATED OUT BY  
AREA OF MEDICAL INTEREST.

11-FEB-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: FDA WORKSHOP PLANS  
CONTACT PERSON: PIERCE, ROSS M.D.  
MEETING RE: REQUEST FOR NAME OF THE HELSINKI  
INVESTIGATOR INVOLVED IN THE QUANTITATIVE ASPECTS  
OF THE LOCAT TRIAL AS WELL AS ANY OTHER EXPERTS  
WITH WHOM WE MAY BE WORKING. HE IS PLANNING AND  
FDA-SPONSORED WORKSHOP ON METHODOLOGY  
STANDARDIZATION IN QUANTITATIVE CORONARY  
ANGIOGRAPHY TRIALS.

14-FEB-91 589 PR. 906-312 CENTERS 17 - 24

21-FEB-91 590 PR. 906-349-14 / NEW PRINCIPLE INVESTIGATOR  
CONTENT:  
PR. 906-349-9  
MITCHELL, WILLIAM M.D.

26-FEB-91 591 LETTER RE: RESPONSE TO FDA REQUEST FOR INFORMATION  
CONTENT:

LETTER TO: LIPICKY, RAYMOND J. M.D.  
CI-906  
TO PROVIDE REQUESTED INFORMATION RE:  
COMPREHENSIVE LIST OF ALL STUDIES TO BE INCLUDED  
IN THE SAFETY DATABASE AND THE LOCATION OF EACH  
STUDY PROTOCOL WHICH HAD BEEN SUBMITTED TO THE  
IND FILE.  
LISTED ARE SEVERAL STUDIES WHICH ARE FOR LOCAL  
REGISTRATION PURPOSES IN EUROPE.  
PROVIDED A TABULAR SUMMARY WHICH PROVIDES AN  
OVERVIEW OF EACH STUDY WHICH WILL HAVE A  
FINALIZED STUDY REPORT IN THE SUPPLEMENTAL  
APPLICATION.  
LIST OF STUDIES CONDUCTED WITH PATIENTS OTHER  
THAN THOSE HAVING HYPERTENSION OR CONGESTIVE  
HEART FAILURE.  
INFORMATION ATTACHED

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28-FEB-91 592 LETTER RE: RESPONSE TO FDA REQUEST FOR INFORMATION  
CONTENT:

LETTER TO: LIPICKY, RAYMOND M.D.  
CI-906  
RE: RESPONDING TO 24-JAN-91 QUESTIONS RECEIVED  
FROM DR. SOMANI ABOUT THE PROTOCOL 906-318.  
ANSWERS TO QUESTION ARE ATTACHED.

05-MAR-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: IND 3-DAY SAFETY REPORT  
CONTACT PERSON: CHEN SHAW DR.  
TELEPHONE CONVERSATION RE: TO ALERT HIM TO A DEATH  
DUE TO AGRANULATYTOSIS IN A PATIENT TREATED WITH  
QUINAPRIL. DETAILS OF THIS CASE ARE ATTACHED.  
WE WOULD PROVIDE WRITTEN REPORT .

08-MAR-91 593 NEW SUB-INVESTIGATOR / STUDY CANCELED  
CONTENT:

PR. 906-311-6  
COLQUHOUN, M. DR.  
  
PR. 906-349-6  
STUDY HAS BEEN CANCELED, NO PATIENTS WERE ENROLLED

12-MAR-91 594 SAFETY REPORT  
CONTENT:

PATIENT NO.: NOT SPECIFIED (N.S.)  
PR. 906 FRENCH POST-MARKETING STUDY  
AE: PATIENT DIED AS A RESULT OF AGRANULOCYTOSIS  
AE 033-0906-910003-00

25-MAR-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: QUINAPRIL NDA  
CONTACT PERSON: TEMPLE, ROBERT DR. VIA TELEPHONE  
SUMMARY: ON MAR-25-91 I RECEIVED A TELEPHONE CALL  
FROM DR. ROBERT TEMPLE REGARDING THE QUINAPRIL  
PHARMACOLOGY REVIEW. I HAD LEFT A MESSAGE WITH HIS  
SECRETARY ON MAR-22-91 STATING THAT WE HAD HEARD  
DR. VAN ARSDALE HAD NOT YET FINISHED HIS REVIEW.  
BOB SAID THAT DR. VAN ARSDALE HAD COMPLETED THE  
REVIEW AND WAS DISCUSSING IT WITH HIS SUPERVISOR,  
DR. RESNICK. HE EXPECTED THAT DR. LIPICKY WOULD  
HAVE IT SHORTLY.  
HE SAID HIS REVIEW TIME SHOULD NOT BE LONG  
DEPENDING UPON OTHER THINGS ON HIS DESK. HE  
COMMENTED THAT HE WAS PRETTY FAMILIAR WITH THE ACE  
INHIBITORS AND IT SHOULD NOT BE ANY PROBLEM.

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28-MAR-91 595 PR. 906-349-13 / PROTOCOL AMENDMENT  
CONTENT:

AMENDMENT NO. 1  
PR. 906-349-13  
DATE: 22-MAR-91  
ADDS ADDITIONAL ASSESSMENTS FOR PATIENTS SAFETY BY  
MEASURING SERUM CREATININE TWICE DURING THE FIRST  
WEEK OF THE DOUBLE-BLIND PHASE OF THE STUDY.

08-APR-91 596 PR. 906-276 CENTERS 30 AND 33  
CONTENT:

CENTER NUMBER 33 WILL PARTICIPATE IN BOTH THE  
OPEN-LABEL AND DOUBLE BLIND PORTION OF THIS STUDY.

18-APR-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: QUESTIONS CONCERNING PROTOCOL 906-43008-0  
(SER. NO. 588, JANUARY 25, 1991)  
CONTACT PERSON: BONGIOVANNI, K. VIA TELEPHONE  
SUMMARY: MS. BONGIOVANNI CALLED CONCERNING THE  
ABOVE PROTOCOL WHICH IS A STUDY OF THE RENAL AND  
METABOLIC EFFECTS OF QUINAPRIL IN NORMOTENSIVE  
PATIENTS WITH NON-INSULIN DEPENDENT DIABETES  
MELLITUS. THE MEDICAL REVIEWER AND STATISTICIAN AT  
FDA HAVE SOME CONCERNS ABOUT ENDPOINTS AND SAMPLE  
SIZE. (THESE WERE NONSPECIFIC CONCERNS AT THIS  
POINT; HOWEVER, MS. BONGIOVANNI SUGGESTED A  
MEETING TO DISCUSS.) MS. BONGIOVANNI ASKED IF THE  
STUDY HAD STARTED YET, TO WHICH I TOLD HER I  
THOUGHT THAT IT HAD. SHE ASSUMED THAT THIS WAS A  
STUDY TO SUPPORT A NEW INDICATION, TO WHICH I  
RESPONDED THAT IT WAS NOT FOR THAT PURPOSE AT ALL.  
SHE BELIEVED THIS MIGHT CHANGE THEIR CONCERN  
SOMEWHAT, BUT WANTED TO KNOW A LITTLE MORE ABOUT  
WHY WE WERE DOING THE STUDY. I SAID I WOULD FIND  
OUT MORE AND RETURN THE CALL.

18-APR-91 597 PR. 906-276-32  
CONTENT:

CENTER NUMBER 32 WILL PARTICIPATE IN BOTH THE  
OPEN-LABEL AND DOUBLE-BLIND PORTION OF THIS STUDY.

24-APR-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: FOLLOW-UP TO QUESTIONS CONCERNING  
906-43008-0 (SEE CONTACT OF APR-18-91).  
CONTACT PERSON: BONGIOVANNI, K. VIA TELEPHONE  
SUMMARY: I CALLED MS. BONGIOVANNI TO FOLLOW-UP ON  
QUESTIONS RECEIVED CONCERNING PROTOCOL 906-43008-0  
ON APRIL 18, 1991. I ASSURED MS. BONGIOVANNI THAT  
WE WERE NOT PURSUING AN INDICATION IN NORMOTEN-  
SIVE DIABETIC PATIENTS. WE VIEW THIS PROTOCOL AS A  
PILOT STUDY. WE FELT THAT THE ORIGINAL PROPOSAL,  
BY A WELL-KNOWN RESEARCHER IN THE U.K., WAS A  
REASONABLE AVENUE OF RESEARCH AND SAW NO REASON  
NOT TO DO A PILOT STUDY. THE REASON THE STUDY WAS

INCLUDED IN THE U.S. IND WAS A CLINICAL SUPPLIES  
SOURCING ISSUE; THE 2.5 MG TABLETS WERE NOT  
AVAILABLE FROM EX - U.S. SOURCES. SHE THANKED ME  
FOR THE INFORMATION AND SEEMED SATISFIED WITH  
OUR RESPONSE.

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DOC DATE	SER/SUPPL NO	TITLE
26-APR-91	598	PR. 906-311-031
CONTENT:		CENTER 31 WILL ALSO PARTICIPATE IN THE OPEN-LABEL PORTION OF THIS STUDY.
26-APR-91	598	NEW SUBINVESTIGATOR / CHANGE IN PROTOCOL
CONTENT:		PR. 906-311-4 SUBINVESTIGATOR LYNCH, S. DR. B.SC, MB, CH.B., MRCP  ON APRIL 8, 1991 (SERIAL NO. 596) WE NOTIFIED YOU OF PROTOCOL 906-276-30. THIS CENTER WILL NOW PARTICIPATE IN THE OPEN-LABEL PORTION OF THIS MULTICENTER STUDY.
17-MAY-91	599	SAFETY REPORT
CONTENT:		PATIENT NI. 001 (EB) PR. 432-906-600-1367 AE: HOSPITALIZED FOR HYPERTENSIVE CRISIS AE NO. 049-0906-910005-00
17-MAY-91	599	SAFETY REPORT
CONTENT:		PATIENT NO. 04 (CK) PR. 423-906-600-0942 AE: HOSPITALIZED FOR HYPERTENSIVE CRISIS AE NO. 049-0906-910008-00
23-MAY-91	600	SAFETY REPORT
CONTENT:		PATIENT NI. 001 (EB) PR. 432-906-600-1367 AE: HOSPITALIZED FOR HYPERTENSIVE CRISIS AE NO. 049-0906-910005-00 FOLLOW-UP SER. NO. 599
23-MAY-91	600	SAFETY REPORT
CONTENT:		PATIENT NO. 04 (CK) PR. 423-906-600-0942 AE: HOSPITALIZED FOR HYPERTENSIVE CRISIS AE NO. 049-0906-910008-00 FOLLOW-UP SER. NO. 599

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DOC DATE SER/SUPPL NO TITLE

23-MAY-91 601 PR. 906-423352 CENTERS 1, 5, AND 7  
CONTENT:

ON APRIL 26, 1991 (SERIAL NO. 598) WE  
INADVERTENTLY MISNUMBERED OUR PROTOCOL 906-311-31.  
THE CORRECT NUMBER IS 906-276-31.

05-JUN-91 LETTER RE: IND AMENDMENT  
CONTENT:

LETTER TO: SPIVEY, R.  
LETTER FROM: LIPICKY, R. M.D.  
RE: PLEASE REFER TO YOUR NEW DRUG APPLICATION  
(IND) SUBMITTED UNDER SECTION 505(I) OF THE  
FEDERAL FOOD, DRUG, AND COSMETIC ACT FOR ACCUPRIL  
(QUINAPRIL HYDROCHLORIDE) TABLETS.  
WE ALSO REFER TO YOUR AMENDMENT DATED JAN. 25,  
1991, SERIAL NUMBER 588.  
WE HAVE COMPLETED OUR REVIEW OF THE PROTOCOL  
ENTITLED, "A THREE-YEAR, DOUBLE-BLIND, PARALLEL-  
GROUP, PLACEBO-CONTROLLED STUDY TO ASSESS THE  
RENAL AND METABOLIC EFFECTS OF ACCUPRO (QUINAPRIL)  
IN NORMOTENSIVE PATIENTS WITH NON-INSULIN  
DEPENDENT DIABETES MELLITUS."  
SHOULD YOU DECIDE TO PURSUE AN INDICATION OF THIS  
TYPE, WE ADVISE YOU TO MEET WITH THE DIVISION TO  
DISCUSS YOUR CLINICAL DEVELOPMENT PLANS. IN  
DESIGNING TRIALS TO DEMONSTRATE PRESERVATION OF  
RENAL FUNCTION, -----  
CONTINUED - SEE CENTRAL FILE COPY.

11-JUN-91 602 RESPONSE TO FDA REQUEST FOR INFORMATION  
CONTENT:

LETTER TO: LIPICKY, RAYMOND M.D.  
LETTER FROM: SPIVEY, RICHARD PHARM.D., PH.D.  
RE: RESPONSE TO FDA REQUEST FOR INFORMATION  
REFERENCE IS MADE TO YOUR LETTER OF JUNE 5, 1991  
AND TO OUR AMENDMENT OF JANUARY 25, 1991 (SERIAL  
NO. 588). THANK-YOU FOR YOUR COMMENTS REGARDING  
THE PROTOCOL SUBMITTED IN THE ABOVE REFERENCED  
AMENDMENT.  
WE ARE NOT CURRENTLY PURSUING AN INDICATION FOR  
QUINAPRIL IN THE TREATMENT OF NORMOTENSIVE  
PATIENTS WITH NON-INSULIN DEPENDENT DIABETES  
MELLITUS. SHOULD WE DECIDE TO PURSUE AN  
INDICATION OF THIS TYPE WE WILL CONTACT THE  
DIVISION TO DISCUSS OUR CLINICAL DEVELOPMENT  
PLANS.  
IF YOU HAVE ANY ADDITIONAL COMMENTS OR QUESTIONS  
PLEASE CONTACT ME AT (313) 996-7061.

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DOC DATE	SER/SUPPL NO.	TITLE
21-JUN-91	603	INFORMATION AMENDMENT
CONTENT:		
		RR 764-01579 AUTHORS: OLSON, S. ET AL DATE: 17-SEP-90 "DISTRIBUTION OF 14C-CI-906 IN TISSUE OF PREGNANT RATS FOLLOWING SINGLE ORAL DOSE"
		RR 745-01754 AUTHOR: BLEAVINS, M.R. DATE: 02-FEB-91 "IN VITRO ANALYTICAL INTERFERENCE TESTING OF CI-906, CI-975, AND CI-9033"
		RR 740-02922 AUTHOR: TAYLOR, D.G. DATE: 30-JAN-91 "QUINAPRIL AND THE PREVENTION OF GENETIC HYPER- TENSION IN THE SPONTANEOUSLY HYPERTENSIVE RAT"
21-JUN-91	603	INFORMATION AMENDMENT - CONTINUED
CONTENT:		
		RR 740-02947 AUTHORS: KEISER, J.A. ET AL DATE: 15-APR-91 "COMPARISON OF ANGIOTENSIN-CONVERTING ENZYME INHIBITORS: EFFECTS ON RENAL FUNCTION IN THE SALT-DEPLETED RAT"
		RR 740-02895 AUTHORS: KEISER, J.A. ET AL DATE: 17-APR-91 "ANTIHYPERTENSIVE EFFECTS OF IV OR ORALLY ADMINISTERED DILTIAZEM IN QUINAPRIL-TREATED SPONTANEOUSLY HYPERTENSIVE RATS"
21-JUN-91	603	INFORMATION AMENDMENT - CONTINUED
CONTENT:		
		RR 740-02936 AUTHORS: BJORK, F. AND KEISER, J. DATE: 03-JUN-91 "VASCULAR BED SELECTIVITY STUDIES WITH QUINAPRIL, CAPTOPRIL, AND ENALAPRIL IN ANESTHETIZED MONGREL DOGS"
		RR 720-02833 AUHTORS: CANTER D.E. ET AL DATE: 02-NOV-90 "A 36-WEEK, OPEN-LABEL EXTENSION OF A 16-WEEK, DOUBLE-BLIND, OPTIONAL-TITRATION, MULTICENTER STUDY COMPARING THE EFFICACY OF ONCE DAILY QUINAPRIL HYDROCHLORIDE WITH TWICE DAILY PROPRANOLOL IN THE TREATMENT OF MILD TO MODERATE HYPERTENSION (PROTOCOL 906-183X)"



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21-JUN-91 603 INFORMATION AMENDMENT - CONTINUED  
CONTENT:

RR 720-02839  
AUTHORS: CANTER, D.A. ET AL  
DATE: 09-NOV-90  
"INITIAL SUMMARY OF RESULTS ON THE DOSE RESPONSE  
RELATIONSHIP, HUMORAL EFFECTS AND  
PHARMACOKINETICS OF QUINAPRIL IN SALT-REPLETE  
NORMOTENSIVE SUBJECTS (PROTOCOL 906-296)"

RR 4301-00062  
AUTHORS: WOELFING A. AND LILIENTHAL, J.  
DATE: 15-FEB-91  
"REPORT OF A 12-WEEK, UNCONTROLLED, OPEN-LABEL  
STUDY TO DETERMINE THE EFFICACY AND SAFETY OF  
ONCE DAILY ORALLY ADMINISTERED QUINAPRIL  
HYDROCHLORIDE (CI-906) IN PATIENTS WITH MILD TO  
MODERATE HYPERTENSION (PROTOCOL 906-246)"

21-JUN-91 603 INFORMATION AMENDMENT - CONTINUED  
CONTENT:

RR 4301-00063  
AUTHORS: LILIENTHAL, J. AND WOELFING, A.  
DATE: 15-FEB-91  
"REPORT OF A 12-WEEK, UNCONTROLLED, OPEN-LABEL  
STUDY TO DETERMINE THE EFFICACY AND SAFETY OF  
ONCE DAILY ORALLY ADMINISTERED QUINAPRIL  
HYDROCHLORIDE (CI-906) WHEN ADDED TO  
HYDROCHLOROTHIAZIDE 25 MG ONCE A DAY IN PATIENTS  
WITH MODERATE TO SEVERE HYPERTENSION (PROTOCOL  
906-247)"

21-JUN-91 603 INFORMATION AMENDMENT - CONTINUED  
CONTENT:

RR 724-00129  
AUTHORS: SEDMAN, A. ET AL  
DATE: 05-APR-91  
"A DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED,  
MULTIPLE-DOSE STUDY OF THE HEMODYNAMIC EFFECTS OF  
QUINAPRIL HCL (CI-906) IN PATIENTS WITH MILD TO  
MODERATE HYPERTENSION (PROTOCOL 906-293)"

RR 744-00040  
AUTHORS: BMMERT, J.A. ET AL  
DATE: 28-APR-91  
"MULTIPLE-DOSE PHARMACOKINETICS OF QUINAPRIL AND  
ITS ACTIVE METABOLITE QUINAPRILAT IN PATIENTS  
WITH CONGESTIVE HEART FAILURE: PROTOCOL 906-256"

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21-JUN-91 603 INFORMATION AMENDMENT - CONTINUED

CONTENT:

ALL SAFETY DATA FORM CLINICAL STUDIES HAVE BEEN  
INCORPORATED IN THE QUINAPRIL THIRD SAFETY UPDATE  
TO NDA 19-885 (19-FEB-91).

THE RESULTS OF THE STUDIES INCLUDED IN THIS  
SUBMISSION DO NOT EFFECT THE CONCLUSION REPORTED  
IN OUR PENDING NDA 19-885.

21-JUN-91 604 PR. 906-371-2

09-JUL-91 605 ANNUAL REPORT

CONTENT:

ISSUE DATE: 01-JUL-91

16-JUL-91 606 PR. 906-423352 CENTERS 2, 3, 4 AND 6

16-JUL-91 606 PROTOCOL AMENDMENT

CONTENT:

AMENDMENT NO. 1

PR. 906-371-0

DATE: 23-APR-91

THIS AMENDMENT CHANGES THE PROTOCOL TITLE TO ALLOW  
COMPASSIONATE USE OF QUINAPRIL FOR PATIENTS  
PREVIOUSLY AND OR CURRENTLY IN QUINAPRIL CHF  
CLINICAL TRIALS FOR WHOM THE USE OF CURRENTLY  
AVAILABLE MARKETED ACE-INHIBITOR THERAPIES IS  
CONTRAINDICATED, INEFFECTIVE OR CAUSES INTOLERABLE  
SIDE EFFECTS.

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01-AUG-91 607 SAFETY REPORT  
CONTENT:

PATIENTS NO. 004/ES  
PR. 423-900-600-0587  
AE: ASTHMATIC BRONCHITIS AFTER APPROXIMATELY TWO  
MONTHS OF QUINAPRIL; PATIENT SUBSEQUENTLY  
RECOVERED.  
AE. NO. 049-0906-910027-00

06-AUG-91 608 LETTER RE: INFORMATION AMENDMENT; CLINCIAL  
CONTENT:

LETTER TO: LIPICKY, RAYMOND M.D.  
LETTER FROM: SPIVEY, RICHARD  
RE: REFERENCE IS MADE TO AN ORIGINAL WRITTEN  
SAFETY REPORT FOR ACCUPRIL (QUINAPRIL  
HYDROCHLORIDE) TABLETS SUBMITTED 01-AUG-91 (SER.  
NO. 607). WE ARE PROVIDING, FOR YOUR INFORMATION,  
A COPY OF THE LETTER WHICH WAS SENT TO  
INVESTIGATORS, NOTIFYING THEM OF A REPORT OF  
ASTHMATIC BRONCHITIS.  
PLEASE INCORPORATE THIS INFORMATION, BY CROSS-  
REFERENCE, INTO OUR PENDING NDA 19-885 FOR  
ACCUPRIL. SHOULD YOU HAVE QUESTIONS-----

20-AUG-91 609 SAFETY REPORT  
CONTENT:

PATIENT NO. 007/CHE  
PR. 955-5-23  
AE: 38 YEAR OLD MALE WHO EXPERIENCED DIARRHEA,  
VOMITING AND FEVER RESULTING IN DEHYDRATION AND  
RENAL FAILURE.  
AE NO. 033-0955-910002-00

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DOC DATE	SER/SUPPL NO	TITLE
13-SEP-91	610	SAFETY REPORT
CONTENT:		
PATIENT NO.: /ED		
PR. 906-		
AE: AUTOIMMUNE HEMOLYTIC ANEMIA		
AE. NO. 033-0906-910010-00		
26-SEP-91	611	PR. 906-375-0
26-SEP-91	612	LETTER RE: INFORMATION AMENDMENT CLINICAL
CONTENT:		
LETTER TO: LIPICKY, RAYMOND MD		
LETTER FROM: SPIVEY, RICHARD		
RE: REFERENCE IS MADE TO AN ORIGINAL WRITTEN		
SAFETY REPORT FOR ACCUPRIL (QUINAPRIL HYDRO-		
CHLORIDE) TABLETS SUBMITTED 13-SEP-91 (SER# 610).		
WE ARE PROVIDING, FOR YOUR INFORMATION, A COPY OF		
THE LETTER WHICH WAS SENT TO INVESTIGATORS,		
NOTIFYING THEM OF A REPORT OF HEMOLYTIC ANEMIA.		
QUESTIONS CALL-----		
16-OCT-91	613	INFORMATION AMENDMENT
CONTENT:		
RR 744-00033		
AUTHORS: BURGER, P.J. ET AL		
DATE: 13-JUN-91		
"A PHARMACOKINETIC STUDY TO DETERMINE WHETHER 10-		
MG AND 20-MG QUINAPRIL HCL TABLETS MANUFACTURED		
IN VEGA BAJA, PUERTO RICO USING FLUID BED DRYING		
ARE BIOEQUIVALENT TO 20-MG QUINAPRIL TABLETS		
MANUFACTURED IN MORRIS PLAINS, NEW JERSEY USING		
OVEN-DRIED GRANULATION: PROTOCOL 906-346"		
16-OCT-91	613	INFORMATION AMENDMENT - CONTINUED
CONTENT:		
RR 4301-00087		
AUTHOR: WOELFING, A.		
DATE: 17-JUN-91		
"REPORT OF A 12-WEEK, UNCONTROLLED, OPEN-LABEL		
STUDY TO DETERMINE THE EFFICACY AND SAFETY OF		
ONCE DAILY 20 MG OR 40 MG ORALLY ADMINISTERED		
QUINAPRIL HYDROCHLORIDE (CI-906) OR 40 MG		
QUINAPRIL HYDROCHLORIDE COMBINED WITH		
HYDROCHLORITHIAZIDE 25 MG (CI-955) ONCE A DAY IN		
PATIENTS WITH MILD TO MODERATE HYPERTENSION		
(PROTOCOL 906-253)"		

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16-OCT-91	613	PROTOCOL AMENDMENT
CONTENT: AMENDMENT NO. 2 PR. 906-351-0 DATE: 12-AUG-91 AMENDMENT CHANGES THE INCLUSION CRITERIA AND SOME LABORATORY DETERMINATIONS.		
31-OCT-91		FDA CONTACT MEMO
CONTENT: MEMO RE: QUESTIONS ON PROTOCOL 906-276 CONTACT PERSON: KENNEMER, E. VIA TELEPHONE MEMO FROM: SPIVEY, R. ABSTRACT: QUESTIONS ON PROTOCOL 906-276.		
13-NOV-91	614	IB UPDATE
CONTENT: DATE: 09-MAY-89 (REVISED 27-SEP-91) RR X-720-02572 AUTHORS: DAWKINS, R. AND PURCELL, T.J. "INVESTIGATOR'S BROCHURE: QUINAPRIL HYDROCHLORIDE (CI-906)" REVISED: 25-OCT-91 THE INFORMATION FOR INVESTIGATOR'S SECTION (PAGES 2-14) HAS BEEN UPDATED GENERALLY, AND NOW INCLUDES ADDITIONAL INFORMATION ON THE USE OF QUINAPRIL IN THE TREATMENT OF CONGESTIVE HEART FAILURE.		

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CI NUMBER= 906 APPL NUMBER= 19-885

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26-JAN-89 1 INITIAL NDA  
CONTENT:

VOLUMES=286

ITEM 1: OVERALL DETAILED INDEX TO NDA 19-885.

ITEM 2: COMPREHENSIVE SUMMARY.

ITEM 3: CHEMISTRY, MANUFACTURING AND CONTROLS.

ITEM 4: SAMPLES, METHODS VALIDATION AND LABELING.

ITEM 5: NON CLINICAL PHARMACOLOGY AND TOXICOLOGY.

RR 740-00929

AUTHOR: KAPLAN, H.R.

DATE: 30-MAR-82

"THE EFFECTS OF ANGIOTENSIN CONVERTING ENZYME  
(ACE) INHIBITORS CI-906 AND CI-907 ON ARTERIAL  
BLOOD PRESSURE AND HEART RATE IN CONSCIOUS RENAL  
HYPERTENSIVE RATS"

26-JAN-89 1 INITIAL NDA - CONTINUED  
CONTENT:

RR 740-00930

AUTHOR: KAPLAN, H.R.

DATE: 12-MAR-82

"SUBACUTE EFFECTS OF ANGIOTENSIN CONVERTING  
ENZYME (ACE) INHIBITOR CI-906 ON BLOOD PRESSURE  
AND HEART RATE IN CONSCIOUS RENAL HYPERTENSIVE  
RATS: A FIVE-DAY STUDY"

RR 740-02483

AUTHOR: RYAN, M.J.

DATE: 7-JUN-88

"ANTI HYPERTENSIVE EFFECTS OF QUINAPRIL DURING A  
FIVE-DAY DOSING STUDY IN RENAL HYPERTENSIVE RATS"

RR 740-02484

AUTHOR: RYAN, M.J.

DATE: 7-JUN-88

"ANTI HYPERTENSIVE ACTIVITY OF QUINAPRIL IN  
HYDROCHLOROTHIAZIDE-TREATED CONSCIOUS  
SPONTANEOUSLY HYPERTENSIVE RATS"

26-JAN-89 1 INITIAL NDA - CONTINUED  
CONTENT:

RR 740-00931

AUTHOR: KAPLAN, H.R. ET AL

DATE: 13-APR-82

"EFFECTS OF ANGIOTENSIN CONVERTING ENZYME (ACE)  
INHIBITORS CI-906 AND CI-907 ON ARTERIAL BLOOD  
PRESSURE AND HEART RATE IN CONSCIOUS  
SPONTANEOUSLY HYPERTENSIVE RATS (SHR): A FIVE-  
DAY STUDY"

RR 740-00936

AUTHORS: SINGER, R.

RYAN, M.

DATE: 23-MAR-82

"PRELIMINARY EVALUATION OF THE ANTI HYPERTENSIVE  
EFFECTS OF ANGIOTENSIN CONVERTING ENZYME  
INHIBITORS IN DE MINORITIC HYPERTENSIVE DOGS"

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26-JAN-89	1	INITIAL NDA - CONTINUED
CONTENT:		<p>RR 740-00938 AUTHORS: SINGER, R. RYAN, M. DATE: 31-MAR-82 "BLOOD PRESSURE LOWERING ACTIVITY OF A NEW NONSULFHYDRYL ANGIOTENSIN CONVERTING ENZYME INHIBITORS, CI-906: COMPARISON WITH MK-421"</p> <p>RR 740-02378 AUTHOR: SINGER, R. ET AL DATE: 16-DEC-87 "EFFECTS OF QUINAPRIL ON BLOOD PRESSURE AND HEART RATE IN DIURETIC-TREATED RENAL HYPERTENSIVE DOGS"</p> <p>RR 740-02377 AUTHOR: SINGER, R. DATE: 4-JAN-88 "EFFECTS OF ENALAPRIL ON BLOOD PRESSURE AND HEART RATE IN DIURETIC-TREATED RENAL HYPERTENSIVE DOGS"</p>
26-JAN-89	1	INITIAL NDA - CONTINUED
CONTENT:		<p>RR 740-00271 AUTHOR: PARKER, R.B. DATE: 13-FEB-79 "METHOD: IN VITRO (BIOCHEMICAL) ASSAY FOR ANGIOTENSIN CONVERTING ENZYME (ACE) AND THE INHIBITION OF ACE"</p> <p>RR 740-00610 AUTHORS: ESSENBURG, A.D. SMITH, R.D. DATE: 28-APR-81 "CN-109,452 INHIBITION OF GUINEA PIG SERUM ANGIOTENSIN CONVERTING ENZYME (ACE) ACTIVITY IN VITRO"</p>
26-JAN-89	1	INITIAL NDA - CONTINUED
CONTENT:		<p>RR 740-00935 AUTHORS: ESSENBURG, A.D. COHEN, D.M. DATE: 30-MAR-82 "IN VITRO INHIBITION OF ANGIOTENSIN CONVERTING ENZYME ACTIVITY WITH CI-906 IN PLASMA FROM NORMOTENSIVE AND HYPERTENSIVE HUMANS"</p> <p>RR 740-00704 AUTHORS: MAJOR, T.C. COHEN, D.M. DATE: 13-APR-82 "THE EFFECTS OF ANGIOTENSIN CONVERTING ENZYME (ACE) INHIBITORS (ND-92275, CN-108182, CN-109326, CN-109325, CN-109452-2K, CN-109438-2, CN-109762-2, AND CN-110021-1A) ON TENSION"</p>

DEVELOPMENT IN ISOLATED RABBIT AND RAT AORTIC  
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26-JAN-89	1	INITIAL NDA - CONTINUED
CONTENT:		
RR 740-00706 AUTHOR: SMITH, R.D. ET AL DATE: 17-AUG-81 "EFFECT OF NC-109,452-2, MK-421, AND CAPTORIL ON THE RESPONSES TO ANGIOTENSIN I, ANGIOTENSIN II, NOREPINEPHRINE AND BRADYKININ IN CONSCIOUS NORMOTENSIVE RATS"		
RR 740-00880 AUTHOR: METZ, T.E. ET AL DATE: 14-JAN-82 "COMPARISON OF THE EFFECTS OF CI-906, CI-907, CAPTOPRIL, AND MK-421 ON THE RESPONSES TO ANGIOTENSIN I, ANGIOTENSIN II, NOREPINEPHRINE, AND BRADYKININ IN CONSCIOUS, NORMOTENSIVE RATS"		
26-JAN-89	1	INITIAL NDA - CONTINUED
CONTENT:		
RR 740-00934 AUTHOR: COHEN, D.M. ET AL DATE: 17-MAR-82 "CORRELATION OF PLASMA ANGIOTENSIN CONVERTING ENZYME (ACE) INHIBITION WITH ANTIHYPERTENSIVE EFFECTS OF CI-906 AND MK-421 (NC-109326-6614) IN RENAL HYPERTENSIVE RATS"		
RR 740-00995 AUTHOR: COHEN, D.M. ET AL DATE: 10-AUG-82 "CORRELATION OF AORTIC AND BRAIN ANGIOTENSIN CONVERTING ENZYME (ACE) INHIBITION WITH ANTIHYPERTENSIVE EFFECTS OF CI-906, AND MK-421 (CN-109326-6614) IN RENAL HYPERTENSIVE RATS"		
26-JAN-89	1	INITIAL NDA - CONTINUED
CONTENT:		
RR 740-01803 AUTHOR: COHEN, D.M. DATE: 22-OCT-85 "EFFECTS OF SEVERAL ACE INHIBITORS ON BRAIN CONVERTING ENZYME ACTIVITY IN NORMOTENSIVE RATS"		
RR 740-00837 AUTHOR: SODERBERG, V. ET AL DATE: 31-MAR-82 "ORAL ANGIOTENSIN CONVERTING ENZYME INHIBITORY ACTIVITY OF CI-906 IN THE CONSCIOUS DOG; COMPARISON WITH MK-421 (ENALAPRIL) AND CAPTOPRIL (SQ-14,225)"		

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26-JAN-89 1 INITIAL NDA - CONTINUED  
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RR 740-01372

AUTHORS: GERMAIN, C.L.  
MERTZ, T.E.

DATE: 24-APR-84

"COMPARISON OF THE EFFECTS OF CI-906, CAPTOPRIL,  
AND ENALAPRIL (ACE INHIBITORS) ON THE BLOOD  
PRESSURE AND HEART RATE RESPONSES TO BRADYKININ  
BEFORE AND AFTER TREATMENT WITH INDOMETHACIN IN  
CONSCIOUS RABBITS"

RR 740-02519

AUTHOR: PACE, D.P. ET AL

DATE: 30-AUG-88

"HEMODYNAMIC RESPONSES TO QUINAPRIL (CI-906) IN  
CONSCIOUS SODIUM-RESTRICTED FUROSEMIDE-TREATED  
DOGS"

26-JAN-89 1 INITIAL NDA - CONTINUED  
CONTENT:

RR 740-00792

AUTHOR: POTOCZAK, R.E. ET AL

DATE: 15-SEP-81

"THE EFFECTS OF CI-906 ON CARDIOVASCULAR FUNCTION  
IN NORMAL CONSCIOUS DOGS"

RR 740-00793

AUTHOR: POTOCZAK, R.E. ET AL

DATE: 15-SEP-81

"THE EFFECTS OF MK-421 ON CARDIOVASCULAR FUNCTION  
IN NORMAL CONSCIOUS DOGS"

RR 740-00502

AUTHOR: POTOCZAK, R.E. ET AL

DATE: 19-MAY-80

"THE EFFECTS OF CAPTOPRIL ON CARDIOVASCULAR  
FUNCTION IN NORMAL CONSCIOUS DOGS"

26-JAN-89 1 INITIAL NDA - CONTINUED  
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RR 740-02158

AUTHORS: STEFFEN, R.P.  
ELDON, C.M.

DATE: 3-MAR-87

"THE HEMODYNAMIC EFFECTS OF THE ANGIOTENSIN  
CONVERTING ENZYME INHIBITOR, CI-928 IN A MODEL  
OF ACUTE PROPRANOLOL INDUCED HEART FAILURE IN  
THE ANESTHETIZED DOG"

RR 740-02520

AUTHOR: KEISER, J.A.

DATE: 22-AUG-88

"THE EFFECTS OF ACUTE INTRAVENOUS ADMINISTRATION  
OF QUINAPRIL AT OR VEHICLE ON RENAL FUNCTION IN  
ANESTHETIZED MORGREL DOGS"

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RR 740-02345  
AUTHORS: STEFFEN, R.P.  
ELDON, C.M.  
DATE: 11-DEC-87  
"EFFECTS OF ANGIOTENSIN-CONVERTING ENZYME (ACE)  
INHIBITORS ON RENAL AND PERIPHERAL HEMODYNAMICS  
AND URINE OUTPUT IN ANESTHETIZED DOG"

RR 740-00932  
AUTHOR: KAPLAN, H.R. ET AL  
DATE: 12-MAR-82  
"SUBACUTE EFFECTS OF ANGIOTENSIN CONVERTING  
ENZYME (ACE) INHIBITOR CI-906 ON BLOOD PRESSURE  
AND HEART RATE IN CONSCIOUS NORMOTENSIVE RATS:  
A SEVEN-DAY STUDY"

26-JAN-89 1 INITIAL NDA - CONTINUED  
CONTENT:

RR MEMO-740-00637  
AUTHOR: STUCKI, W.P.  
DATE: 28-APR-81  
"EX VIVO PLATELET AGGREGATION STUDIES ON  
CN-109452-2"

RR 740-00713  
AUTHOR: UHLENDORF, P.D.  
DATE: 18-MAY-81  
"LIPID REGULATING EFFECT OF THE ANTIHYPERTENSIVE  
AGENT CN-109,452"

RR 740-01706  
AUTHOR: UHLENDORF, P.D. ET AL  
DATE: 30-JUN-86  
"LIPID-REGULATING EFFECT OF CI-906, CI-907, AND  
CI-925 IN CHOLESTEROL-FED RATS: COMPARISON TO  
REFERENCE ACE INHIBITORS"

26-JAN-89 1 INITIAL NDA - CONTINUED  
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RR 740-02001  
AUTHOR: KRAUSE, B. ET AL  
DATE: 14-NOV-86  
"THE EFFECT OF QUINAPRIL ON PLASMA LIPID  
CONCENTRATIONS IN NORMAL RATS: COMPARISON TO  
REFERENCE ACE INHIBITORS"

RR 740-02456  
AUTHOR: KRAUSE, B.R. ET AL  
DATE: 6-JUN-88  
"EFFECT OF QUINAPRIL, CAPTOPRIL, AND ENALAPRIL  
IN FRUCTOSE-FED RATS"

RR 740-01931  
AUTHOR: KRAUSE, B. ET AL  
DATE: 1-III-86

"THE EFFECTS OF BEVANTOLOL ON PLASMA LIPID  
CONCENTRATIONS IN NORMAL RATS: COMPARISON TO  
REFERENCE ANTIHYPERTENSIVE AGENTS"

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26-JAN-89 1 INITIAL NDA - CONTINUED  
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RR 740-02528  
AUTHOR: KRAUSE, B.R. ET AL  
DATE: 2-AUG-88  
"EFFECT OF ACE INHIBITORS ON PLASMA LIPIDS IN  
NORMAL RATS: CONFIRMATION OF TRIGLYCERIDE-  
LOWERING EFFECT USING ORAL DOSING"

RR 740-00940  
AUTHORS: BURMEISTER, W.E.  
KAPLAN, H.R.  
DATE: 16-APR-82  
"THE EFFECTS OF CI-906, MK-421, AND CAPTOPRIL  
ON BARORECEPTOR REFLEX HEART RATE RESPONSES IN  
THE ALPHA-CHLORALASE ANESTHETIZED DOG MODEL"

RR 740-00646  
AUTHOR: KINKEL, M.  
DATE: 23-MAR-81  
"A PULMONARY SAFETY STUDY WITH INTRAVENOUS  
CN-109452 IN THE ANESTHETIZED DOG"

26-JAN-89 1 INITIAL NDA - CONTINUED  
CONTENT:

RR 740-00649  
AUTHORS: FINKEL, M.  
FOSTER, T.  
DATE: 1-JUN-81  
"A PULMONARY RISK ASSESSMENT OF CN-109452-2L"

RR 740-00742  
AUTHOR: MERTZ, T.E. ET AL  
DATE: 24-JUN-81  
"AUTONOMIC EVALUATION OF THE ANGIOTENSIN  
CONVERTING ENZYME INHIBITOR ANTIHYPERTENSIVE  
AGENTS CN-109452, CAPTOPRIL, AND MK 421"

RR 740-00747  
AUTHOR: MERTZ, T.E ET AL  
DATE: 24-JUN-81  
"SELECTIVE INHIBITION OF ANGIOTENSIN I AND  
POTENTIATION OF BRADYKININ BY CN-109452,  
CAPTOPRIL, AND MK421 IN ANESTHETIZED DOGS"

26-JAN-89 1 INITIAL NDA - CONTINUED  
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RR 740-00666  
AUTHOR: LABAY, R.J. ET AL  
DATE: 4-MAY-81  
"EFFECTS OF CN-109452-2 IN THE CNS SURVEY"

RR 740-00647  
AUTHORS: WILEY, J.N.  
DOWNS, D.A.  
DATE: 19-MAR-81  
"EVALUATION OF CN-109452-2K IN MOUSE ACTIVITY AND  
INVERTED SCREEN TEST (MAST)"

RR 740-00860

AUTHORS: BOHNER, B.L.  
          DOWNS, D.A.

DATE: 30-NOV-81

"THE EFFECT OF CN-109452-2K IN THE PHARMACOLOGICAL  
RIST TEST"

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RR 740-00687  
AUTHORS: VARTANIAN, M.  
POSCHER, P.  
DATE: 4-MAY-81  
"EFFECTS OF CN-109452-2L ON CONSUMMATORY BEHAVIOR"

RR 740-00652  
AUTHORS: NINTEMAN, F.  
SMITH, M.  
DATE: 4-MAY-81  
"THE EFFECT OF CN-109,452-2L ON SELF-STIMULATING  
RATS"

RR 740-02311  
AUTHOR: DAVIS, R.E.  
DATE: 3-DEC-87  
"EFFECT PD 109452 (CI-906), AN ANGIOTENSIN  
CONVERTING ENZYME INHIBITOR (ACE), ON BODY  
TEMPERATURE AND SURVIVAL TIME UNDER  
NORMABARIC HYPOXIA IN MICE"

26-JAN-89 1 INITIAL NDA - CONTINUED  
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RR 740-02313  
AUTHOR: DAVIS, R.E.  
DATE: 8-DEC-87  
"REVERSAL OF ECS-INDUCED AMNESIA BY ANGIOTENSIN  
CONVERTING ENZYME INHIBITORS (ACE) IN WEANING  
RATS"

RR 740-02312  
AUTHOR: DAVIS, R.E.  
DATE: 3-DEC-87  
"EFFECTS OF CI-906 (PD 109452), AN ANGIOTENSIN  
CONVERTING ENZYME INHIBITOR (ACE), ON DELAYED  
ALTERNATION PERFORMANCE IN RATS"

26-JAN-89 1 INITIAL NDA - CONTINUED  
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RR 740-01319  
AUTHOR: WILEY, J.N. ET AL  
DATE: 9-FEB-84  
"EVALUATION OF CI-906, CI-907, AND CI-925,  
POTENTIAL ACE INHIBITORS, AND REFERENCE DRUGS  
CAPTOPRIL AND ENALAPRIL IN THE MOUSE  
ANTIWRITHING TEST"

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26-JAN-89 1 INITIAL NDA - CONTINUED  
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RR 740-00698  
AUTHOR: COUGHENOUR, L.L. ET AL  
DATE: 26-JUN-81  
"THE AFFINITY OF CN-109452-2 (CI-906) AND  
CAPTOPRIL FOR VARIOUS NEUROTRANSMITTER RECEPTORS  
IN RAT BRAIN"

RR 740-02301  
AUTHORS: WEISHAAR, R.E.  
ESSENBERG, A.D.  
DATE: 24-JUL-87  
"EFFECT OF PD 127751-2 ON THE ACTIVITY OF  
ANGIOTENSIN CONVERTING ENZYME"

RR 740-02355  
AUTHORS: WEISHAAR, R.E.  
ESSENBERG, A.D.  
DATE: 4-JAN-88  
"EFFECT OF PD 109452-2 AND REFERENCE AGENTS ON THE  
ACTIVITY OF ANGIOTENSIN CONVERTING ENZYME"

26-JAN-89 1 INITIAL NDA - CONTINUED  
CONTENT:

RR 740-02354  
AUTHORS: WIESHAAR, R.E.  
ESSENBERG, A.D.  
DATE: 4-JAN-88  
"EFFECT OF PD 109489-2K AND REFERENCE AGENTS ON  
THE ACTIVITY OF ANGIOTENSIN CONVERTING ENZYME"

RR 740-02290  
AUTHOR: RYAN, M.J.  
DATE: 24-JUL-87  
"THE EFFECTS OF ORAL ADMINISTRATION OF PD 127,751  
ON ARTERIAL BLOOD PRESSURE AND HEART RATE IN  
CONSCIOUS RENAL HYPERTENSIVE RATS"

RR 740-02369  
AUTHOR: RYAN, M.J.  
DATE: 13-NOV-87  
"THE EFFECTS OF ORAL ADMINISTRATION OF PD 109489-2  
ON ARTERIAL BLOOD PRESSURE AND HEART RATE IN  
CONSCIOUS RENAL HYPERTENSIVE RATS"

26-JAN-89 1 INITIAL NDA - CONTINUED  
CONTENT:

RR 740-02152  
AUTHOR: RYAN, M.J.  
DATE: 24-FEB-87  
"THE EFFECTS OF ORAL ADMINISTRATION OF THE  
ANGIOTENSIN CONVERTING ENZYME (ACE) INHIBITOR  
CI-928 ON ARTERIAL BLOOD PRESSURE AND HEART  
RATE IN CONSCIOUS GOLDBLATT HYPERTENSIVE RATS"

RR 740-02357  
AUTHORS: WEISHAAR, R.E.  
ESSENBERG, A.D.



DATE: 4-JAN-88

"EFFECT OF PD 118854 AND REFERENCE AGENTS ON THE  
ACTIVITY OF ANGIOTENSIN CONVERTING ENZYME"

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26-JAN-89 1 INITIAL NDA - CONTINUED  
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RR 740-02367

AUTHOR: RYAN, M.J. ET AL

DATE: 12-NOV-87

"THE EFFECTS OF ORAL ADMINISTRATION OF PD 118854-2  
ON ARTERIAL BLOOD PRESSURE AND HEART RATE IN  
CONSCIOUS RENAL HYPERTENSIVE RATS"

RR 740-02356

AUTHORS: WEISHAAR, R.E.

ESSENBERG, A.D.

DATE: 4-JAN-88

"EFFECT OF PD 126130 AND REFERENCE AGENTS ON THE  
ACTIVITY OF ANGIOTENSIN CONVERTING ENZYME"

RR 740-02368

AUTHOR: RYAN, M.J. ET AL

DATE: 13-NOV-87

"THE EFFECTS OF ORAL ADMINISTRATION OF PD 126130-2  
ON ARTERIAL BLOOD PRESSURE AND HEART RATE IN  
CONSCIOUS RENAL HYPERTENSIVE RATS"

26-JAN-89 1 INITIAL NDA - CONTINUED  
CONTENT:

RR 740-2291

AUTHORS: WEISHAAR, R.E.

ESSENBURG, A.D.

DATE: 24-JUL-87

"EFFECT OF PD 109488 ON THE ACTIVITY OF  
ANGIOTENSIN CONVERTING ENZYME"

RR 740-02353

AUTHORS: WEISHAAR, R.E.

ESSENBERG, A.D.

DATE: 11-DEC-87

"EFFECT OF PD 113413 AND REFERENCE AGENTS ON THE  
ACTIVITY OF ANGIOTENSIN CONVERTING ENZYME"

26-JAN-89 1 INITIAL NDA - CONTINUED  
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RR 740-02283

AUTHOR: RYAN, M.J. ET AL

DATE: 14-JUL-87

"THE EFFECTS OF ORAL ADMINISTRATION OF PD 109488  
ON ARTERIAL BLOOD PRESSURE AND HEART RATE IN  
CONSCIOUS SPONTANEOUSLY HYPERTENSIVE AND RENAL  
HYPERTENSIVE RATS"

RR 745-00433

AUTHOR: KIM, S.N. ET AL

DATE: 31-AUG-81

"ACUTE ORAL TOXICITY STUDY OF CI-906 IN MALE AND  
FEMALE ALBINO MICE"

RR 250-01303

AUTHOR: BARSOUM, N.J.

DATE: 15-MAR-82

"ACUTE ORAL TOXICITY STUDY OF CI-906  
(PD 109452-2) IN MICE"

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RR 250-01332  
AUTHOR: BARSOUM, N.J. ET AL  
DATE: 26-AUG-83  
"ACUTE ORAL TOXICITY STUDY OF CI-906 (PD 109452-2)  
IN MICE"

RR 250-01516  
AUTHOR: MACALLUM, G.E. ET AL  
DATE: 9-NOV-87  
"ACUTE INTRAVENOUS TOXICITY STUDY OF CI-906  
(PD 109452-2) IN MICE"

RR MEMO-745-00426  
AUTHOR: SANYER, J.L. ET AL  
DATE: 25-AUG-81  
"PRELIMINARY DOSE RANGE FINDING ACUTE ORAL  
TOXICITY STUDY OF CI-906 IN MALE AND FEMALE  
ALBINO RATS"

26-JAN-89 1 INITIAL NDA - CONTINUED  
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RR 745-00427  
AUTHOR: SANYER, J.L. ET AL  
DATE: 28-AUG-81  
"ACUTE ORAL TOXICITY STUDY OF CI-906 IN MALE AND  
FEMALE ALBINO RATS"

RR 745-00459  
AUTHOR: ANDERSON, J.A. ET AL  
DATE: 22-JAN-82  
"ACUTE INTRAVENOUS TOXICITY STUDY OF CI-906  
IN MALE AND FEMALE ALBINO RATS"

RR 250-01515  
AUTHOR: MACALLUM, G.E.  
DATE: 9-NOV-87  
"ACUTE INTRAVENOUS TOXICITY STUDY OF CI-906  
(PD 109452-2) IN RATS:

26-JAN-89 1 INITIAL NDA - CONTINUED  
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RR 745-00441  
AUTHOR: WATKINS, J.R. ET AL  
DATE: 27-OCT-81  
"EXPLORATORY ORAL RISING DOSE STUDY IN BEAGLE  
DOGS WITH CI-906"

RR 250-01338  
AUTHOR: BARSOUM, N.J. ET AL  
DATE: 2-DEC-83  
"14 DAY REPEATED DOSE ORAL TOXICITY STUDY OF  
CI-906 IN MICE"

RR 745-00779  
AUTHOR: LAVASEKADA, M.H. ET AL

DATE: 5-DEC-84

"THIRTEEN-WEEK MOUSE ORAL RANGE FINDING STUDY:  
CI-906"

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RR 745-00333

AUTHOR: SANYER, J.L. ET AL

DATE: 3-MAR-82

"TWO-WEEK EXPLORATORY ORAL TOXICITY STUDY OF  
CI-906 IN MALE AND FEMALE ALBINO RATS"

RR 745-00479

AUTHOR: WATKINS, J.R. ET AL

DATE: 4-MAR-82

"TWO WEEK ORAL TOXICITY STUDY OF CI-906 IN MALE  
AND FEMALE ALBINO RATS"

RR 745-00552

AUTHOR: KIM, S.N. ET AL

DATE: 29-DEC-82

"THIRTEEN-WEEK ORAL TOXICITY STUDY OF CI-906 IN  
MALE AND FEMALE ALBINO RATS"

26-JAN-89 1 INITIAL NDA - CONTINUED  
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RR 745-00686

AUTHOR: ANDERSON, J.A. ET AL

DATE: 16-APR-84

"52-WEEK ORAL TOXICITY STUDY AND 104-WEEK  
CARCINOGEN BIOASSAY OF CI-906 IN RATS -  
26-WEEK SUMMARY REPORT"

RR 745-00776

AUTHOR: ANDERSON, J.A. ET AL

DATE: 18-DEC-84

"52-WEEK ORAL TOXICITY STUDY AND 104-WEEK  
CARCINOGEN BIOASSAY OF CI-906 IN RATS -  
52-WEEK SUMMARY REPORT"

RR 745-00460

AUTHOR: MCGUIRE, E.J. ET AL

DATE: 25-FEB-82

"TWO-WEEK ORAL TOXICITY STUDY OF CI-906 IN  
BEAGLE DOGS"

26-JAN-89 1 INITIAL NDA - CONTINUED  
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RR 745-00539

AUTHOR: ANDERSON, J.A. ET AL

DATE: 20-DEC-82

"13-WEEK ORAL TOXICITY STUDY OF CI-906 IN BEAGLE  
DOGS"

RR 745-00716

AUTHOR: JAYASEKARA, M.U. ET AL

DATE: 14-MAY-84

"52-WEEK ORAL TOXICITY STUDY OF CI-906 IN BEAGLE  
DOGS - 26-WEEK SUMMARY REPORT"

RR 745-00767

AUTHOR: JAYASEKARA, M.U. ET AL

DATE: 18-DEC-84

"52-WEEK ORAL TOXICITY STUDY OF CI-906 IN BEAGLE  
DOGS"

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CONTENT:

RR 745-00749

AUTHOR: ANDERSON, J.A. ET AL

DATE: 17-SEP-84

"FERTILITY AND REPRODUCTION STUDIES IN RATS WITH  
CI-906"

RR 745-00541

AUTHOR: ANDERSON, J.A. ET AL

DATE: 9-DEC-82

"TERATOLOGY STUDY IN RATS WITH CI-906"

RR 745-00527

AUTHOR: KIM, S.N. ET AL

DATE: 1-OCT-82

"EXPLORATORY DOSE RANGE-FINDING STUDY IN RABBITS  
WITH CI-906"

26-JAN-89 1 INITIAL NDA - CONTINUED  
CONTENT:

RR 745-00608

AUTHOR: ANDERSON, J.A. ET AL

DATE: 20-JUN-83

"EXPLORATORY RANGE-FINDING TERATOLOGY STUDY IN  
RABBITS WITH CI-906"

RR 745-00639

AUTHOR: ANDERSON, J.A. ET AL

DATE: 11-OCT-83

"TERATOLOGY STUDY IN RABBITS (CI-906)

RR 745-00844

AUTHOR: ANDERSON, J.A.

DATE: 13-SEP-85

"PERINATAL AND POSTNATAL STUDY IN RATS WITH  
CI-906"

26-JAN-89 1 INITIAL NDA - CONTINUED  
CONTENT:

RR 745-00412

AUTHOR: LAKE, R.S. ET AL

DATE: 29-MAY-81

"STANDARD BACTERIAL MUTAGENICITY PLATE ASSAY OF  
CN-109452"

RR 745-00523

AUTHOR: ANDERSON, J.A. ET AL

DATE: 2-AUG-82

"IN VITRO POINT MUTATION ASSAY OF CI-906 IN  
CHINESE HAMSTER LUNG CELLS"

RR 745-00529

AUTHOR: MOYER, C.E. ET AL

DATE: 1-OCT-82

"IN VITRO SISTER-CHROMATID EXCHANGE (SCE) ASSAY  
OF CI-906 IN CHINESE HAMSTER OVARY (CHO) CELLS"



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26-JAN-89 1 INITIAL NDA - CONTINUED  
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RR 745-01168  
AUTHOR: KROPKO, M.L. ET AL  
DATE: 14-SEP-87  
"IN VITRO CHROMOSOMAL ABERRATION ASSAY OF CI-906  
IN V79 CHINESE HAMSTER LUNG CELLS"

RR 745-01156  
AUTHOR: KRISHNA, G. ET AL  
DATE: 14-SEP-87  
"MOUSE MICRONUCLEUS STUDY OF CI-906"

26-JAN-89 1 INITIAL NDA - CONTINUED  
CONTENT:

RR 745-00764  
AUTHOR: PARADISO, L.J. ET AL  
DATE: 5-DEC-84  
"ACUTE INTRAVENOUS TOXICITY OF CI-928 IN MALE  
AND FEMALE B6C3F1 MICE"

RR 745-00687  
AUTHOR: CARMODY, L.P. ET AL  
DATE: 28-FEB-84  
"ACUTE EXPLORATORY INTRAVENOUS TOXICITY OF CI-928  
IN MALE AND FEMALE ALBINO RATS"

RR 745-00747  
AUTHOR: PEGG, D.G. ET AL  
DATE: 27-AUG-84  
"EXPLORATORY INTRAVENOUS RISING DOSE STUDY IN  
BEAGLE DOGS WITH CI-928 (PD 109,548)"

26-JAN-89 1 INITIAL NDA - CONTINUED  
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RR 250-01466  
AUTHOR: MACALLUM, G.E. ET AL  
DATE: 5-NOV-86  
"EXPLORATORY 2 WEEK DAILY REPEATED DOSE  
INTRAVENOUS TOXICITY STUDY OF CI-928  
(PD 109548) IN RATS"

RR 250-01476  
AUTHOR: MACALLUM, G.E. ET AL  
DATE: 16-JAN-87  
"4 WEEK DAILY REPEATED DOSE INTRAVENOUS TOXICITY  
STUDY OF CI-928 (PD 109548) IN RATS"

RR 250-01475  
AUTHOR: MACALLUM, G.E.  
DATE: 16-JAN-87  
"EXPLORATORY 2 WEEK INTRAVENOUS TOXICITY STUDY OF  
CI-928 (PD 109548) IN BEAGLE DOGS"

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26-JAN-89 1 INITIAL NDA - CONTINUED  
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RR 250-01483  
AUTHOR: MACALLUM, G.E. ET AL  
DATE: 23-FEB-87  
"4 WEEK REPEATED DOSE INTRAVENOUS TOXICITY STUDY  
OF CI-928 (PD 109548) IN BEAGLE DOGS"

RR 745-00986  
AUTHOR: NELSON, D.R. ET AL  
DATE: 12-DEC-86  
"INTRAVENOUS IRRITATION STUDY IN RABBITS WITH  
CI-928"

RR 745-00976  
AUTHOR: NELSON, D.R. ET AL  
DATE: 22-OCT-86  
"INTR-ARTERIAL TOLERANCE STUDY IN RABBITS WITH  
CI-928"

26-JAN-89 1 INITIAL NDA - CONTINUED  
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RR 745-00633  
AUTHOR: KIM, S.N. ET AL  
DATE: 18-OCT-83  
"STANDARD BACTERIAL MUTAGENICITY PLATE ASSAY OF  
CI-928"

RR 745-00892  
AUTHOR: PEGG, D.G.  
DATE: 12-DEC-85  
"ACUTE ORAL TOXICITY STUDY OF PD 109,488 IN  
B6C3F1 MICE"

RR 745-00891  
AUTHOR: PEGG, D.G. ET AL  
DATE: 12-DEC-85  
"ACUTE ORAL TOXICITY STUDY OF PD 109,488 IN MALE  
AND FEMALE ALBINO RATS"

26-JAN-89 1 INITIAL NDA - CONTINUED  
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RR 745-01220  
AUTHOR: DETHLOFF, L.A. ET AL  
DATE: 6-MAY-88  
"ACUTE INTRAVENOUS TOXICITY STUDY OF PD 109,488 IN  
MALE AND FEMALE ALBINO RATS"

RR 745-01221  
AUTHOR: DETHLOFF, L.A. ET AL  
DATE: 8-APR-88  
"ACUTE INTRAVENOUS TOXICITY STUDY OF PD 113,413  
AND MALE AND FEMALE ALBINO RATS"

RR 901-00052  
AUTHOR: FASSULIOTIS, K. ET AL  
DATE: 16-JUN-86

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RR 901-00076  
AUTHOR: FASSULIOTIS, K. ET AL  
DATE: 16-JUN-86  
"ACUTE ORAL TOXICITY (DL50) STUDY OF PD 107438-2  
S-1,2,3,4-TETRAHYDROISOQUINOLINE-3-CARBOXYLIC  
ACID HYDROCHLORIDE)) IN RATS FOR OCCUPATIONAL  
HEALTH HAZARD EVALUATION"

RR 745-01179  
AUTHOR: ANDREWS, L.K. ET AL  
DATE: 22-DEC-87  
"ACUTE ORAL TOXICITY STUDY OF PD 127,751-2 IN  
WISTAR RATS"

RR 720-01435  
AUTHOR: BARSOUM, N.J. ET AL  
DATE: 21-JAN-86  
"ACUTE ORAL TOXICITY STUDY OF CI-939 IN MICE"

26-JAN-89 1 INITIAL NDA - CONTINUED  
CONTENT:

RR 250-01432  
AUTHOR: BARDOUM, N.J. ET AL  
DATE: 21-JAN-86  
"ACUTE ORAL TOXICITY STUDY OF CI-939 IN RATS"

RR 250-01437  
AUTHOR: BARSOUM, N.J. ET AL  
DATE: 21-JAN-86  
"EXPLORATORY ORAL RISING DOSE TOXICITY STUDY OF  
CI-939 IN BEAGLE DOGS"

RR 250-01445  
AUTHOR: BARSOUM, N.J. ET AL  
DATE: 3-APR-86  
"EXPLORATORY 4 WEEK DAILY REPEATED DOSE ORAL  
TOXICITY STUDY OF CI-939 IN RATS"

26-JAN-89 1 INITIAL NDA - CONTINUED  
CONTENT:

RR 250-01511  
AUTHORS: GREAVES, P.  
DE LA IGLESIA, F.A.  
DATE: 10-NOV-87  
"FIFTEEN WEEK ORAL TOXICITY STUDY WITH CI-939  
IN RATS"

RR 250-01509  
AUTHORS: GREAVES, P.  
DE LA IGLESIA, F.A.  
DATE: 3-NOV-87  
"16 DAY ORAL TOXICITY STUDY OF CI-939 IN BEAGLE  
DOGS"

RR 250-01517

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26-JAN-89	1	INITIAL NDA - CONTINUED
CONTENT:		<p>RR 250-01471 AUTHOR: ROGERS, S.C. ET AL DATE: 8-JUL-87 "ACUTE ORAL TOXICITY STUDY OF CI-955 (QUINAPRIL-HYDROCHLOROTHIAZIDE COMBINATION) IN MICE"</p> <p>RR 250-01484 AUTHOR: ROBERS, S.C. ET AL DATE: 8-JUL-87 "ACUTE ORAL TOXICITY STUDY OF CI-955 (QUINAPRIL-HYDORCHOROTHIAZIDE COMBINATION) IN RATS"</p> <p>RR MEMO-764-00943 AUTHOR: HORVATH, A.M. ET AL DATE: 29-JAN-88 "PLASMA CI-928 AND HYDROCHLOROTHIAZIDE (CI-570) CONCENTRATIONS IN DOGS DURING A EXPLORATORY RISING-DOSE TOXICOLOGY STUDY WITH COMBINATION PRODUCT CI-955 - SHERIDAN PARK TOXICOLOGY STUDY 1353"</p>
26-JAN-89	1	INITIAL NDA - CONTINUED
CONTENT:		<p>RR 250-01507 AUTHOR: ROGERS, S.C. ET AL DATE: 18-AUG-87 "13 WEEK DAILY REPEATED DOSE ORAL TOXICITY STUDY OF CI-955 IN RATS"</p> <p>RR MEMO-764-00946 AUTHOR: OLSON, S.C. ET AL DATE: 19-JAN-88 "PLASMA CI-928 AND HYDROCHLOROTHIAZIDE (CI-570) CONCENTRATIONS IN RATS DURING 13 WEEKS OF ORAL DOSING WITH THE COMBINATION PRODUCT CI-955 - SHERIDAN PARK TOXICOLOGY STUDY 1363"</p> <p>RR 250-01497 AUTHOR: ROGERS, S.C. ET AL DATE: 9-JUN-87 "EXPLORATORY 2 WEEK TOXICITY STUDY OF CI-955 IN BEAGLE DOGS"</p>
26-JAN-89	1	INITIAL NDA - CONTINUED
CONTENT:		<p>RR MEMO-764-00936 AUTHOR: HORVATH, A.M. ET AL DATE: 19-JAN-88 "CI-928 AND HYDROCHLOROTHIAZIDE (CI-570) PLASMA CONCENTRATIONS IN MALE AND FEMALE BEAGLE DOGS FOLLOWING ORAL DOSING WITH THE COMBINATION PRODUCT CI-955 - SHERIDAN PARK TOXICOLOGY STUDY 1362"</p>

RR 250-01510

AUTHOR: ROGERS, S.C. ET AL

DATE: 10-SEP-87  
"13 WEEK ORAL TOXICITY STUDY OF CI-955 IN BEAGLE  
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26-JAN-89 1 INITIAL NDA - CONTINUED  
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RR MEMO-764-00944  
AUTHOR: OLSON, S.C. ET AL  
DATE: 3-FEB-88  
"PLASMA CI-928 AND HYDROCHLOROTHIAZIDE (CI-570)  
CONCENTRATIONS IN DOGS DURING 13-WEEK ORAL DOSING  
WITH THE COMBINATION PRODUCT CI-955 - SHERIDAN  
PARK TOXICOLOGY STUDY 1365"

RR MEMO 730-00115  
AUTHOR: HUANG, C.C.  
DATE: 17-AUG-81  
"SYNTHESIS OF CI-906-14C"

RR 740-00271  
AUTHOR: PARKER, R.B.  
DATE: 13-FEB-79  
"METHOD: IN VITRO (BIOCHEMICAL) ASSAY FOR  
ANGIOTENSIN CONVERTING ENZYME (ACE) AND THE  
INHIBITION OF ACE"

26-JAN-89 1 INITIAL NDA - CONTINUED  
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RR 764-00460  
AUTHOR: NORDLOM, G. ET AL  
DATE: 29-OCT-85  
"DEVELOPMENT OF A RADIOIMMUNOASSAY FOR CI-928,  
THE DIACID METABOLITE OF CI-906"

RR MEMO-4192-00302  
AUTHOR: ANHUT, H. ET AL  
DATE: 28-AUG-87  
"CI-928 RADIOIMMUNOASSAY, VALIDATION FOR HUMAN  
PLASMA"

RR 764-00441  
AUTHOR: TAYLOR, M. ET AL  
DATE: 13-FEB-86  
"CI-906 AND CI-928: A VALIDATED GAS  
CHROMATOGRAPHIC ASSAY FOR HUMAN PLASMA SAMPLES"

26-JAN-89 1 INITIAL NDA - CONTINUED  
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RR 764-01083  
AUTHOR: BURGER, P.J. ET AL  
DATE: 24-AUG-88  
"A VALIDATED GAS CHROMATOGRAPHIC METHOD TO  
DETERMINE CI-906 AND ITS ACTIVE METABOLITE,  
CI-928, IN HUMAN URINE"

RR 4192-00292  
AUTHORS: HENGY, H.  
MOST, M.  
DATE: 31-JUL-87  
"VALIDATION OF HIGH-PERFORMANCE LIQUID  
CHROMATOGRAPHIC ASSAY FOR THE DETERMINATION

OF CI-906 AND CI-928 IN HUMAN PLASMA"

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26-JAN-89 1 INITIAL NDA - CONTINUED  
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RR MEMO-4192-00286

AUTHORS: HENGY, H.

MOST, M.

DATE: 18-MAY-87

"CI-906 AND CI-928 CONCENTRATION IN URINE OBTAINED  
FROM THE DIGOXIN/QUINAPRIL-INTERACTIO STUDY (MUN  
683/CI-906-209). VALIDATED HPLC-ASSAY FOR  
CI-906 AND CI-928 IN URINE"

RR 764-01099

AUTHOR: OLSON, S.C. ET AL

DATE: 31-AUG-88

"COMPARISON AND SUMMARY OF ANALYTICAL METHODS USED  
TO CHARACTERIZE QUINAPRIL (CI-906) AND ITS ACTIVE  
METABOLITE, QUINAPRILAT (CI-928), IN PRECLINICAL  
PHARMACOKINETIC STUDIES"

26-JAN-89 1 INITIAL NDA - CONTINUED  
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RR 764-01094

AUTHOR: OLSON, S.C. ET AL

DATE: 31-AUG-88

"COMPARISON AND SUMMARY OF ANALYTICAL METHODS  
USED TO CHARACTERIZE QUINAPRIL (CI-906) AND ITS  
ACTIVE METABOLITE, QUINAPRILAT (CI-928), IN  
CLINICAL PHARMACOKINETIC STUDIES"

RR 764-00188

AUTHOR: BORONDY, P.E. ET AL

DATE: 28-FEB-84

"CI-906-14C: METABOLIC DISPOSITION STUDIES IN  
RATS AND MONKEYS, STABILITY TO DEESTERIFICATION  
AND ACE INHIBITION IN VITRO"

RR 740-00769

AUTHOR: WONG, A. ET AL

DATE: 13-AUG-81

"BIOPHARMACEUTICAL PROFILE OF CI-906 (CN-109,452)"

26-JAN-89 1 INITIAL NDA - CONTINUED  
CONTENT:

RR 764-00275

AUTHORS: TOOTHAKER, R.D.

MEHTA, S.

DATE: 3-OCT-84

"BIOPHARMACEUTICAL PROFILE OF CI-928"

RR 764-00001

AUTHORS: BORONDY, P.E.

MICHNIEWICZ, B.M.

DATE: 6-JAN-82

"CI-906-14C: PRELIMINARY PHARMACOKINETIC AND  
METABOLIC DISPOSITION STUDIES IN LABORATORY  
ANIMALS."



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RR 764-00652  
AUTHOR: FERRY, J.J. ET AL  
DATE: 12-NOV-86  
"BIOAVAILABILITY AND PHARMACOKINETICS OF QUINAPRIL  
(CI-906) AND ITS ACTIVE METABOLITE (CI-928)  
FOLLOWING SINGLE ORAL AND INTRAVENOUS QUINAPRIL  
AND CI-928 DOSES ADMINISTERED TO BEAGLE DOGS"

RR 4192-00347  
AUTHOR: NEUB, M. ET AL  
DATE: 10-AUG-88  
"DOSE PROPORTIONALITY OF QUINAPRIL, QUINAPRILAT  
(CI-928), AND TWO ADDITIONAL METABOLITES  
(PD 109488 AND PD 113413) FOLLOWING ORAL  
QUINAPRIL DOSES OF 25, 50, AND 100 MG/KG IN  
BEAGLE DOGS. PRECLINICAL PROTOCOL NO. 86045"

26-JAN-89 1 INITIAL NDA - CONTINUED  
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RR 764-00606  
AUTHOR: FERRY, J.J. ET AL  
DATE: 6-AUG-86  
"SINGLE DOSE STUDY TO ASSESS THE POTENTIAL DRUG-  
DRUG INTERACTION OF QUINAPRIL (CI-906) AND  
HYCROCHLOROTHIAZIDE (CI-570) IN BEAGLE DOGS"

RR 764-00867  
AUTHOR: OLSON, S.C. ET AL  
DATE: 2-OCT-87  
"PHARMACOKINETIC DISPOSITION OF 14C-QUINAPRIL AND  
ITS ACTIVE METABOLITES, CI-928, AFTER SINGLE AND  
MULTIPLE ORAL DOSES OF QUINAPRIL TO HEALTHY  
VOLUNTEERS, PROTOCOL 906-60"

26-JAN-89 1 INITIAL NDA - CONTINUED  
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RR 764-01104  
AUTHOR: KUGLER, A.R. ET AL  
DATE: 10-OCT-88  
"DEVELOPMENT AND APPLICATION OF AN EQUILIBRIUM  
DIALYSIS METHOD TO DETERMINE QUINAPRIL AND  
QUINAPRILAT PROTEIN BINDING CHARACTERISTICS"

RR 764-00786  
AUTHOR: MCNALLY, W. ET AL  
DATE: 27-APR-87  
"WHOLE-BODY AUTORADIOGRAPHIC ANALYSIS OF TISSUE  
DISTRIBUTION OF 14C-CI-906 IN RATS"

RR 764-00268  
AUTHORS: JORDAN, R.A.  
CHANG, T.  
DATE: 27-AUG-84  
"THE EFFECT OF REPEATED ADMINISTRATION OF CI-906  
ON THE RAT LIVER MICROSOMAL DRUG METABOLISM"

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RR MEMO-764-00916  
AUTHOR: MICHNIEWICZ, B. ET AL  
DATE: 30-NOV-87  
"METABOLIC DISPOSITION OF 14C QUINAPRIL IN RATS"

RR MEMO-764-00917  
AUTHOR: MICHNIEWICZ, B. ET AL  
DATE: 30-NOV-87  
"CHARACTERIZATION OF QUINAPRIL METABOLITES IN  
URINE OF MAN AND DOG FOLLOWING ADMINISTRATION  
OF 14C QUINAPRIL"

RR MEMO-764-01085  
AUTHOR: HORVATH, A.M. ET AL  
DATE: 26-AUG-88  
"THE PHARMACOKINETICS OF THE DIKETOPIPERAZINE  
METABOLITE OF QUINAPRIL HCL, PD 109488, AND THE  
DIKETOPIPERAZINE METABOLITE OF QUINAPRILAT, PD  
113413, IN PATIENTS WITH VARYING DEGREES OF  
RENAL FUNCTION - PROTOCOL 906-255"

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ITEM 6: HUMAN PHARMACOKINETICS AND  
BIOAVAILABILITY.

RR MEMO-730-00115  
AUTHOR: HUANG, C.C.  
DATE: 17-AUG-81  
"SYNTHESIS OF CI-906-14C"

RR 740-00271  
AUTHOR: PARKER, R.B.  
DATE: 13-13-FEB-79  
"METHODS: IN VITRO (BIOCHEMICAL) ASSAY FOR  
ANGIOTENSIN CONVERTING ENZYME (ACE) AND THE  
INHIBITION OF ACE"

RR 764-00460  
AUTHOR: NORDBLOM, G.  
DATE: 29-OCT-85  
"DEVELOPMENT OF A RADIOIMMUNOASSAY FOR CI-928, THE  
DIACID METABOLITE OF CI-906:

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RR MEMO-4192-00302  
AUTHOR: ANHUT, H. ET AL  
DATE: 28-AUG-87  
"CI-928 RADIOIMMUNOASSAY, VALIDATION FOR HUMAN  
PLASMA"

RR 4192-00292  
AUTHORS: HENGY, H.  
MOST, M.  
DATE: 31-JUL-87  
"VALIDATION OF HIGH-PERFORMANCE LIQUID

CHROMATOGRAPHIC ASSAY FOR THE DETERMINATION OF  
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RR MEMO-4192-00286  
AUTHORS: HENGY, G.  
MOST, M.  
DATE: 18-MAY-87  
"CI-906 AND CI-928 CONCENTRATION IN URINE OBTAINED  
FROM THE DIGOXIN/QUINAPRIL-INTERACTION STUDY  
(MUN 683/CI-906-209). VALIDATED HPLC-ASSAY FOR  
CI-906 AND CI-928 IN URINE.

RR 764-00441  
AUTHOR: TAYLOR, M. ET AL  
DATE: 13-FEB-86  
"CI-906 AND CI-928: A VALIDATED GAS  
CHROMATOGRAPHIC ASSAY FOR HUMAN PLASMA SAMPLES"

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RR 764-01083  
AUTHOR: BURGER, P.J. ET AL  
DATE: 24-AUG-88  
"A VALIDATED GAS CHROMATOGRAPHIC METHOD TO  
DETERMINE CI-906 AND ITS ACTIVE METABOLITE,  
CI-928, IN HUMAN URINE"

RR 764-01099  
AUTHOR: OLSON, S.C. ET AL  
DATE: 31-AUG-88  
"COMPARISON AND SUMMARY OF ANALYTICAL METHODS USED  
TO CHARACTERIZE QUINAPRIL (CI-906) AND ITS ACTIVE  
METABOLITE, QUINAPRILAT (CI-928), IN PRECLINICAL  
PHARMACOKINETIC STUDIES"

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RR 764-01094  
AUTHOR: OLSON, S.C. ET AL  
DATE: 31-AUG-88  
"COMPARISON AND SUMMARY OF ANALYTICAL METHODS  
USED TO CHARACTERIZE QUINAPRIL (CI-906) AND ITS  
ACTIVE METABOLITE, QUINAPRILAT (CI-928), IN  
CLINICAL PHARMACOKINETIC STUDIES"

RR 724-00036  
AUTHORS: LATTS, J.R.  
GOULET, J.R.  
DATE: 23-MAR-84  
"A CLINIAL PHARMACOLOGIC STUDY OF CI-906 HCL  
SOLUTION, PROTOCOL 906-2"

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RR 764-00156  
AUTHOR: GRYCZKO, C. ET AL  
DATE: 30-NOV-83  
"ACE INHIBITOR LEVELS IN PLASMA FOLLOWING PERORAL  
ADMINISTRATION OF CI-906 TO NORMAL HUMAN  
VOLUNTEERS. PROTOCOL 906-2"

RR 724-00034  
AUTHOR: LATTS, J.R. ET AL  
DATE: 3-AUG-84  
"REPORT OF A DOUBLE-BLIND, PLACEBO-CONTROLLED  
STUDY OF THE PHARMACOKINETICS AND TOLERANCE OF  
CI-906 HCL IN NORMAL HEALTHY SUBJECTS (PROTOCOL  
906-5)"

26-JAN-89 1 INITIAL NDA - CONTINUED  
CONTENT:

RR 764-00856  
AUTHOR: OLSON, S.C. ET AL  
DATE: 2-SEP-87  
"CLINICAL DOSE PROPORTIONALITY STUDY OF QUINAPRIL  
(CI-906) AND ITS ACTIVE METABOLITE (CI-928)  
FOLLOWING 2.5-MG TO 80-MG SINGLE CAPSULE DOSES  
OF QUINAPRIL, PROTOCOL 906-191"

RR 764-00970  
AUTHOR: HORVATH, A.M. ET AL  
DATE: 5-FEB-88  
"CLINICAL DOSE-PROPORTIONALITY STUDY OF QUINAPRIL  
(CI-906) AND ITS ACTIVE METABOLITE (CI-928)  
FOLLOWING SINGLE 2.5-MG TO 80-MG TABLET DOSES OF  
QUINAPRIL, PROTOCOL 906-259"

26-JAN-89 1 INITIAL NDA - CONTINUED  
CONTENT:

RR 724-00085  
AUTHOR: BERGHOFF, W. ET AL  
DATE: 8-DEC-88  
"REPORT OF A RANDOMIZED, DOUBLE-BLIND, PLACEBO-  
CONTROLLED TOLERANCE AND PHARMACOKINETIC STUDY  
OF SINGLE AND MULTIPLE ORAL DOSES OF QUINAPRIL  
HYDROCHLORIDE (CI-906) IN NORMAL SUBJECTS  
(PROTOCOL 906-254-0)"

RR 764-01104  
AUTHOR: KUGLER, A.R. ET AL  
DATE: 10-OCT-88  
"DEVELOPMENT AND APPLICATION OF AN EQUILIBRIUM  
DIALYSIS METHOD TO DETERMINE QUINAPRIL AND  
QUINAPRILAT PROTEIN BINDING CHARACTERISTICS"

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26-JAN-89 1 INITIAL NDA - CONTINUED  
CONTENT:

RR 764-00867  
AUTHOR: OLSON, S.C. ET AL  
DATE: 2-OCT-87  
"PHARMACOKINETICS DISPOSITION OF 14C-QUINAPRIL AND  
ITS ACTIVE METABOLITS, CI-928 AFTER SINGLE AND  
MULTIPLE ORAL DOSES OF QUINAPRIL TO HEALTHY  
VOLUNTEERS, PROTOCOL 906-60"

RR 764-00917  
AUTHOR: MICHNIEWICZ, B. ET AL  
DATE: 30-NOV-87  
"CHARACTERIZATION OF QUINAPRIL METABOLITES IN  
URINE OF MAN AND DOG FOLLOWING ADMINISTRATION  
OF 14C QUINAPRIL"

26-JAN-89 1 INITIAL NDA - CONTINUED  
CONTENT:

RR 720-02349  
AUTHOR: FRANK, G.J. ET AL  
DATE: 20-NOV-87  
"REPORT OF A COMPARATIVE PHARMACOKINETIC STUDY OF  
ONCE-DAILY ORALLY ADMINISTERED QUINAPRIL  
HYDROCHLORIDE (CI-906) IN YOUNG SUBJECTS AND  
ELDERLY PATIENTS WITH MILD TO MODERATE  
HYPERTENSION (906-223)"

RR 4192-00338  
AUTHOR: NEUB, M. ET AL  
DATE: 24-AUG-88  
"PHARMACOKINETICS OF QUINAPRIL (CI-906) AND  
QUINAPRILAT (CI-928) FOLLOWING SINGLE AND MULTIPLE  
ORAL DOSES IN YOUNG AND ELDERLY VOLUNTEERS,  
PROTOCOL 906-222"

26-JAN-89 1 INITIAL NDA - CONTINUED  
CONTENT:

RR 764-01014  
AUTHOR: OLSON, S.C.  
DATE: 8-APR-88  
"MULTIPLE ORAL DOSE PHARMACOKINETICS OF QUINAPRIL  
(CI-906) AND ITS ACTIVE METABOLITE (CI-928) IN  
RENAL FAILURE - PROTOCOL 906-AE (906-292)"

RR 764-01084  
AUTHOR: HORVATH, A.M. ET AL  
DATE: 25-AUG-88  
"THE PHARMACOKINETICS OF QUINAPRIL HCL AND ITS  
ACTIVE METABOLITE (QUINAPRILAT) IN PATIENTS WITH  
VARYING DEGREES OF RENAL FUNCTION - PROTOCOL  
906-255"

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26-JAN-89 1 INITIAL NDA - CONTINUED  
CONTENT:

RR MEMO-764-01085  
AUTHOR: HORVATH, A.M. ET AL  
DATE: 26-AUG-88  
"THE PHARMACOKINETICS OF THE DIKETOPIPERAZINE  
METABOLITE OF QUINAPRIL HCL, PD 109488, AND THE  
DIKETOPIPERAZINE METABOLITE OF QUINAPRILAT,  
PD 113413, IN PATIENTS WITH VARYING DEGREES OF  
RENAL FUNCTION - PROTOCOL 906-255"

RR 764-00861  
AUTHOR: OLSON, S.C. ET AL  
DATE: 29-OCT-87  
"SINGLE ORAL DOSE PHARMACOKINETICS OF QUINAPRIL  
(CI-906) AND ITS ACTIVE METABOLITE (CI-928) IN  
PATIENTS WITH HEPATIC IMPAIRMENT SECONDARY TO  
ALCOHOL-INDUCED CIRRHOSIS - PROTOCOL 9-032-0"

26-JAN-89 1 INITIAL NDA - CONTINUED  
CONTENT:

RR MEMO-764-00554  
AUTHORS: FERRY, J.  
COLBURN, W.  
DATE: 30-APR-86  
"PHARMACOKINETIC ASSESSMENT OF CI-928 FOLLOWING  
MULTIPLE DOSE ADMINISTRATION OF CI-906 TO  
PATIENTS WITH MILD TO MODERATE HYPERTENSION.  
PROTOCOLS 906: 12-22"

RR MEMO-720-02386  
AUTHOR: BERGHOFF, W.  
DATE: 18-AUG-88  
"REPORT OF A COMPARISON OF QUINAPRIL (CI-906) AND  
CI-928 PLASMA CONCENTRATIONS WITH REDUCTION IN  
DIASTOLIC BLOOD PRESSURE DURING A 12-WEEK DOUBLE-  
BLIND STUDY IN PATIENTS WITH MODERATE TO SEVERE  
HYPERTENSION (PROTOCOLS 906-82 THROUGH 906-87,  
906-89 THROUGH 906-91, 906-93, 906-95, AND  
906-96)"

26-JAN-89 1 INITIAL NDA - CONTINUED  
CONTENT:

RR 764-00779  
AUTHOR: FERRY, J.J. ET AL  
DATE: 24-APR-87  
"SINGLE DOSE PHARMACOKINETIC DRUG-DRUG INTERACTION  
STUDY OF QUINAPRIL (CI-906) AND  
HYDROCHLOROTHIAZIDE (CI-570) IN HEALTHY  
VOLUNTEERS. PROTOCOL 906-211"

RR 764-00820  
AUTHOR: HORVATH, A.M. ET AL  
DATE: 26-JUN-87  
"EFFECT OF MULTIPLE-DOSE PROPRANOLOL  
ADMINISTRATION OF SINGLE-DOSE PHARMACOKINETICS  
OF QUINAPRIL AND ITS ACTIVE METABOLITE (CI-928)



IN HEALTHY VOLUNTEERS. PROTOCOL 906-229"

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26-JAN-89 1 INITIAL NDA - CONTINUED  
CONTENT:

RR 764-00792  
AUTHOR: FERRY, J.J. ET AL  
DATE: 8-JUN-87  
"EFFECT OF QUINAPRIL ON THE MULTIPLE DOSE  
PHARMACOKINETICS OF DIGOXIN IN HEALTHY  
VOLUNTEERS, PROTOCOL 906-209"

RR 764-00663  
AUTHOR: FERRY, J.J. ET AL  
DATE: 5-JAN-87  
"EFFECT OF CIMETIDINE ON SINGLE DOSE  
PHARMACOKINETICS OF QUINAPRIL AND ITS ACTIVE  
METABOLITE (CI-928) IN HEALTHY VOLUNTEERS.  
PROTOCOL 906-113"

26-JAN-89 1 INITIAL NDA - CONTINUED  
CONTENT:

RR 764-00870  
AUTHOR: OLSON, S.C. ET AL  
DATE: 6-OCT-87  
"EFFECT OF QUINAPRIL ON WARFARIN-INDUCED REDUCTION  
IN PROTHROBIN COMPLEX ACTIVITY IN HEALTHY  
SUBJECTS - PROTOCOL 906-235"

RR 764-00872  
AUTHOR: OLSON, S.C. ET AL  
DATE: 1-OCT-87  
"EFFECT OF MAGNESIUM-CONTAINING QUINAPRIL  
TABLETS ON THE SINGLE-DOSE PHARMACOKINETICS OF  
TETRACYCLINE IN HEALTHY VOLUNTEERS, PROTOCOL  
906-237"

26-JAN-89 1 INITIAL NDA - CONTINUED  
CONTENT:

RR 764-00635  
AUTHOR: FERRY, J.J. ET AL  
DATE: 14-JAN-87  
"CLINICAL BIOEQUIVALENCE STUDY COMPARING THREE  
QUINAPRIL CAPSULES AND A QUINAPRIL ORAL SOLUTION.  
PROTOCOL 906-99"

RR 764-00740  
AUTHOR: FERRY, J.J. ET AL  
DATE: 17-FEB-87  
"CLINICAL BIOAVAILABILITY STUDY COMPRING TWO  
PROTOTYPE QUINAPRIL TABLET FORMULATIONS, A  
QUINAPRIL CAPSULE FORMULATION, AND A QUINAPRIL  
ORAL SOLUTION, PROTOCOL 906-202"

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26-JAN-89 1 INITIAL NDA - CONTINUED  
CONTENT:

RR 764-00771

AUTHOR: HORVATH, A.M. ET AL

DATE: 13-APR-87

"CLINICAL BIOAVAILABILITY STUDY COMPARING TWO  
PROTOTYPE QUINAPRIL TABLET FORMULATIONS AND A  
QUINAPRIL CAPSULE FORMULATION, PROTOCOL 906-234"

RR 764-00887

AUTHOR: HORVATH, A.M. ET AL

DATE: 2-NOV-87

"SINGLE-DOSE BIOEQUIVALENCE STUDY COMPARING  
QUINAPRIL 5- AND 40-MG MARKET-IMAGE TABLETS AND  
QUINAPRIL 20-MG CAPSULES IN HEALTHY VOLUNTEERS -  
PROTOCOL 906-230"

26-JAN-89 1 INITIAL NDA - CONTINUED  
CONTENT:

RR 764-00808

AUTHOR: FERRY, J.J. ET AL

DATE: 26-JUN-87

"SINGLE-DOSE BIOEQUIVALENCE STUDY COMPARING  
QUINAPRIL 2.5-MG MARKET-IMAGE TABLETS AND  
QUINAPRIL 20-MG CAPSULES IN HEALTHY VOLUNTEERS,  
PROTOCOL 906-239"

RR 764-00556

AUTHOR: FERRY, J. ET AL

DATE: 11-JUN-86

"EFFECT OF FOOD ON CI-906 (QUINAPRIL) AND CI-928  
PHARMACOKINETICS FOLLOWING ORAL DOSING OF CI-906  
TO HEALTHY SUBJECTS. PROTOCOL 906-80"

26-JAN-89 1 INITIAL NDA - CONTINUED  
CONTENT:

ITEM 8: CLINICAL DATA

RR 724-00036

AUTHORS: LATTS, J.R.

GOULET, J.R.

DATE: 23-MAR-84

"A CLINICAL PHARMACOLOGIC STUDY OF CI-906 HCL  
SOLUTION, PROTOCOL 906-2"

RR MEMO-764-00156

AUTHOR: GRYCZKO, C. ET AL

DATE: 30-NOV-83

"ACE INHIBITOR LEVELS IN PLASMA FOLLOWING PERORAL  
ADMINISTRATION OF CI-906 TO NORMAL HUMAN  
VOLUNTEERS. PROTOCOL 906-2"

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26-JAN-89 1 INITIAL NDA - CONTINUED  
CONTENT:

RR MEMO-764-00131  
AUTHORS: BORONDY, P.E.  
EASTON, M.E.  
DATE: 6-JUN-83  
"INHIBITION OF PLASMA ANGIOTENSIN CONVERTING  
ENZYME (ACE) ACTIVITY FOLLOWING PERORAL  
ADMINISTRATION OF CI-906 TO NORMAL HUMAN  
VOLUNTEERS. PROTOCOL CI-906-2"

RR 724-00034  
AUTHOR: LATTS, J.R. ET AL  
DATE: 3-AUG-84  
"REPORT OF A DOUBLE-BLIND, PLACEBO-CONTROLLED  
STUDY OF THE PHARMACOKINETICS AND TOLERANCE OF  
CI-906 HCL IN NORMAL HEALTHY SUBJECTS (PROTOCOL  
906-5)"

26-JAN-89 1 INITIAL NDA - CONTINUED  
CONTENT:

RR 764-00856  
AUTHOR: OLSON, S.C. ET AL  
DATE: 2-SEP-87  
"CLINICAL DOSE PROPORTIONALITY STUDY OF QUINAPRIL  
(CI-906) AND ITS ACTIVE METABOLITE (CI-928)  
FOLLOWING 2.5-MG TO 80-MG SINGLE CAPSULE DOSE OF  
QUINAPRIL, PROTOCOL 906-191"

RR 764-00970  
AUTHOR: HORVATH, A.M. ET AL  
DATE: 5-FEB-88  
"CLINICAL DOSE-PROPORTIONALITY STUDY OF QUINAPRIL  
(CI-906) AND ITS ACTIVE METABOLITE (CI-928)  
FOLLOWING SINGLE 2.5-MG TO 80-MG TABLET DOSES OF  
QUINAPRIL, PROTOCOL 906-259"

26-JAN-89 1 INITIAL NDA - CONTINUED  
CONTENT:

RR MEMO-764-01061  
AUTHORS: OLSON, S.C.  
COLBURN, W.A.  
DATE: 20-JUL-88  
"A PRELIMINARY ESTIMATE OF THE EFFECTIVE  
ACCUMULATION HALF-LIFE FOR QUINAPRILAT"

RR 724-00085  
AUTHOR: BERGHOFF, W. ET AL  
DATE: 8-DEC-88  
"REPORT OF A RANDOMIZED, DOUBLE-BLIND, PLACEBO-  
CONTROLLED TOLERANCE AND PHARMACOKINETIC STUDY  
OF SINGLE AND MULTIPLE ORAL DOSES OF QUINAPRIL  
HYDROCHLORIDE (CI-906) IN NORMAL SUBJECTS  
(PROTOCOL 906-254-0)"

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26-JAN-89 1 INITIAL NDA - CONTINUED  
CONTENT:

RR 764-01104

AUTHOR: KUGLER, A.R. ET AL

DATE: 10-OCT-88

"DEVELOPMENT AND APPLICATION OF AN EQUILIBRIUM  
DIALYSIS METHOD TO DETERMINE QUINAPRIL AND  
QUINAPRILAT PROTEIN BINDING CHARACTERISTICS"

RR 764-00867

AUTHOR: OLSON, S.C. ET AL

DATE: 2-OCT-87

"PHARMACOKINETIC DISPOSITION OF <sup>14</sup>C-QUINAPRIL AND  
ITS ACTIVE METABOLITE, CI-928, AFTER SINGLE AND  
MULTIPLE ORAL DOSES OF QUINAPRIL TO HEALTHY  
VOLUNTEERS, PROTOCOL 906-60"

26-JAN-89 1 INITIAL NDA - CONTINUED  
CONTENT:

RR MEMO-764-00917

AUTHOR: MICHNIEWICZ, B. ET AL

DATE: 30-NOV-87

"CHARACTERIZATION OF QUINAPRIL METABOLITES IN  
URINE OF MAN AND DOG FOLLOWING ADMINISTRATION OF  
<sup>14</sup>C QUINAPRIL"

RR 720-02349

AUTHOR: FRANK, G.J. ET AL

DATE: 20-NOV-87

"REPORT OF A COMPARATIVE PHARMACOKINETICS STUDY OF  
ONCE-DAILY ORALLY ADMINISTERED QUINAPRIL  
HYDROCHLORIDE (CI-906) IN YOUNG SUBJECTS AND  
ELDERLY PATIENTS WITH MILD TO MODERATE  
HYPERTENSION (906-223)"

26-JAN-89 1 INITIAL NDA - CONTINUED  
CONTENT:

RR 4192-00338

AUTHOR: NEUB, M. ET AL

DATE: 24-AUG-88

"PHARMACOKINETICS OF QUINAPRIL (CI-906) AND  
QUINAPRILAT (CI-928) FOLLOWING SINGLE AND  
MULTIPLE ORAL DOSES IN YOUNG AND ELDERLY  
VOLUNTEERS, PROTOCOL 906-222"

RR 764-01014

AUTHOR: OLSON, S.C. ET AL

DATE: 8-APR-88

"MULTIPLE ORAL DOSE PHARMACOKINETICS OF QUINAPRIL  
(CI-906) AND ITS ACTIVE METABOLITE (CI-928) IN  
RENAL FAILURE - PROTOCOL 906-AE (906-292)"

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26-JAN-89 1 INITIAL NDA - CONTINUED  
CONTENT:

RR 764-01084  
AUTHOR: HORVATH, A.M. ET AL  
DATE: 25-AUG-88  
"THE PHARMACOKINETICS OF QUINAPRIL HCL AND ITS  
ACTIVE METABOLITE (QUINAPRILAT) IN PATIENTS WITH  
VARYING DEGREES OF RENAL FUNCTION - PROTOCOL  
906-255"

RR MEMO-764-01085  
AUTHOR: HORVATH, A.M. ET AL  
DATE: 260-AUG-88  
"THE PHARMACOKINETICS OF THE DIKETOPIPERAZINE  
METABOLITE OF QUINAPRIL HCL, PD 109488, AND  
DIKETOPIPERAZINE METABOLITE OF QUINAPRILAT,  
PD 113413, IN PATIENTS WITH VARYING DEGREES OF  
RENAL FUNCTION - PROTOCOL 906-255"

26-JAN-89 1 INITIAL NDA - CONTINUED  
CONTENT:

RR 764-00861  
AUTHOR: OLSON, S.C. ET AL  
DATE: 29-OCT-87  
"SINGLE ORAL DOSE PHARMACOKINETICS OF QUINAPRIL  
(CI-906) AND ITS ACTIVE METABOLITE (CI-928) IN  
PATIENTS WITH HEPATIC IMPAIRMENT SECONDARY TO  
ALCOHOL-INDUCED CIRRHOSIS - PROTOCOL 9-032-0"

RR 764-00779  
AUTHOR: FERRY, J.J. ET AL  
DATE: 24-APR-87  
"SINGLE DOSE PHARMACOKINETIC DRUG-DRUG  
INTERACTION STUDY OF QUINAPRIL (CI-906) AND  
HYDROCHLOROTHIAZIDE (CI-570) IN HEALTHY  
VOLUNTEERS. PROTOCOL 906-211"

26-JAN-89 1 INITIAL NDA - CONTINUED  
CONTENT:

RR 764-00820  
AUTHOR: HORVATH, A.M. ET AL  
DATE: 26-JUN-87  
"EFFECT OF MULTIPLE-DOSE PROPRANOLOL  
ADMINISTRATION OF SINGLE-DOSE PHARMACOKINETICS  
OF QUINAPRIL AND ITS ACTIVE METABOLITE (CI-928)  
IN HEALTHY VOLUNTEERS. PROTOCOL 906-229"

RR 764-00792  
AUTHOR: FERRY, J.J. ET AL  
DATE: 8-JUN-87  
"EFFECT OF QUINAPRIL ON THE MULTIPLE DOSE  
PHARMACOKINETICS OF DIGOXIN IN HEALTHY  
VOLUNTEERS, PROTOCOL 906-209"

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26-JAN-89	1	INITIAL NDA - CONTINUED
CONTENT:		<p>RR 764-00663 AUTHOR: FERRY, J.J. ET AL DATE: 5-JAN-87 "EFFECT OF CIMETIDINE ON SINGLE DOSE PHARMACOKINETICS OF QUINAPRIL AND ITS ACTIVE METABOLITE (CI-928) IN HEALTHY VOLUNTEERS. PROTOCOL 906-113"</p> <p>RR 764-00870 AUTHOR: OLSON, S.C. ET AL DATE: 6-OCT-87 "EFFECT OF QUINAPRIL ON WARFARIN-INDUCED REDUCTION IN PROTHROMBIN COMPLEX ACTIVITY IN HEALTHY SUBJECTS - PROTOCOL 906-235"</p>
26-JAN-89	1	INITIAL NDA - CONTINUED
CONTENT:		<p>RR 764-00872 AUTHOR: OLSON, S.C. ET AL DATE: 1-OCT-87 "EFFECT OF MAGNESIUM-CONTAINING QUINAPRIL TABLETS ON THE SINGLE-DOSE PHARMACOKINETICS OF TETRACYCLINE IN HEALTHY VOLUNTEERS, PROTOCOL 906-237"</p> <p>RR 764-00635 AUTHOR: FERRY, J.J. ET AL DATE: 14-JAN-87 "CLINICAL BIOEQUIVALENCE STUDY COMPARING THREE QUINAPRIL CAPSULES AND A QUINAPRIL ORAL SOLUTION. PROTOCOL 906-99"</p>
26-JAN-89	1	INITIAL NDA - CONTINUED
CONTENT:		<p>RR 764-00740 AUTHOR: FERRY, J.J. ET AL DATE: 17-FEB-87 "CLINICAL BIOAVAILABILITY STUDY COMPARING TWO PROTOTYPE QUINAPRIL TABLET FORMULATIONS, A QUINAPRIL CAPSULE FORMULATION, AND A QUINAPRIL ORAL SOLUTION, PROTOCOL 906-202"</p> <p>RR 764-00771 AUTHOR: HORVATH, A.M. ET AL DATE: 13-APR-87 "CLINICAL BIOAVAILABILITY STUDY COMPARING TWO PROTOTYPE QUINAPRIL TABLET FORMULATIONS AND A QUINAPRIL CAPSULE FORMULATION, PROTOCOL 906-234"</p>

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26-JAN-89 1 INITIAL NDA - CONTINUED  
CONTENT:

RR 764-00887  
AUTHOR: HORVATH, A.M. ET AL  
DATE: 2-NOV-87  
"SINGLE-DOSE BIOEQUIVALENCE STUDY COMPARING  
QUINAPRIL 5- AND 40-MG MARKET-IMAGE TABLETS AND  
QUINAPRIL 20-MG CAPSULES IN HEALTHY VOLUNTEERS -  
PROTOCOL 906-230"

RR 764-00808  
AUTHOR: FERRY, J.J. ET AL  
DATE: 26-JUN-87  
"SINGLE-DOSE BIOEQUIVALENCE STUDY COMPARING  
QUINAPRIL 2.5-MG MARKET-IMAGE TABLETS AND  
QUINAPRIL 20-MG CAPSULES IN HEALTHY VOLUNTEERS,  
PROTOCOL 906-239"

26-JAN-89 1 INITIAL NDA - CONTINUED  
CONTENT:

RR 764-00556  
AUTHOR: FERRY, J. ET AL  
DATE: 11-JUN-86  
"EFFECT OF FOOD ON CI-906 (QUINAPRIL) IND CI-928  
PHARMACOKINETICS FOLLOWING ORAL DOSING OF CI-906  
TO HEALTHY SUBJECTS. PROTOCOL 906-80"

RR 724-00028  
AUTHOR: PEARSE, S.B.  
DATE: 18-FEB-83  
"A STUDY OF THE EFFECTS OF CI-906, IN INHIBITOR OF  
ANGIOTENSIN CONVERTING ENZYME, ON THE RENIN-  
ANGIOTENSIN-ALDOSTERONE SYSTEM AND RELATED  
CARDIOVASCULAR RESPONSES AFTER ANGIOTENSIN-1  
CHALLENGE. PART 1: DOSE-RANGING STUDY IN TWO  
HEALTHY MEN. PART 2: DURATION OF ACTION STUDY  
IN FIVE HEALTHY MEN. {PROTOCOL 906-1 (P.197)}

26-JAN-89 1 INITIAL NDA - CONTINUED  
CONTENT:

RR MEMO-764-00303  
AUTHOR: GRYCZKO, C. ET AL  
DATE: 18-DEC-84  
"ACE INHIBITOR LEVELS IN PLASMA FOLLOWING PERORAL  
ADMINISTRATION OF CI-906 TO NORMAL HUMAN  
VOLUNTEERS AFTER ANGIOTENSIN-1 CHALLENGE.  
PROTOCOL 906-1"

RR 724-00039  
AUTHORS: GOULET, J.R.  
LATTS, J.R.  
DATE: 24-OCT-84  
"REPORT OF A STUDY TO DETERMINE THE EFFECTIVE DOSE  
AND SAFETY OF CI-906 HCL IN PATIENTS WITH MILD  
TO MODERATE UNCOMPLICATED HYPERTENSION (PROTOCOL  
906-4)"



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26-JAN-89 1 INITIAL NDA - CONTINUED  
CONTENT:

RR 724-00041

AUTHORS: LATTS, J.R.  
GOULET, J.R.

DATE: 10-JAN-85

"REPORT OF A STUDY TO DETERMINE THE SAFETY AND  
MINIMUM ANTIHYPERTENSIVE DOSE OF CI-906 HCL  
(PROTOCOL 906-3)"

RR 724-00051

AUTHOR: GOULET, J.R. ET AL

DATE: 21-MAR-85

"REPORT OF PROTOCOLS 906-6 AND -8: A 28-DAY  
DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL OF THE  
EFFICACY OF QUINAPRIL HYDROCHLORIDE (CI-906) IN  
THE TREATMENT OF MILD TO MODERATE HYPERTENSION;  
AND PROTOCOL 906-10, A LONG-TERM EXTENSION OF  
PROTOCOL 906-6"

26-JAN-89 1 INITIAL NDA - CONTINUED  
CONTENT:

RR MEMO-764-00293

AUTHORS: TOOTHAKER, R.D.  
MEHTA, S.

DATE: 9-JAN-85

"ACE INHIBITOR LEVELS IN SERUM FOLLOWING MULTIPLE  
PERORAL DOSES OF CI-906 TO HYPERTENSIVE PATIENTS.  
PROTOCOL 906-6"

RR MEMO-764-00312

AUTHORS: TOOTHAKER, R.D.  
MEHTA, S.

DATE: 26-DEC-84

"ACE INHIBITOR LEVELS IN SERUM FOLLOWING MULTIPLE  
PERORAL DOSES OF CI-906 TO HYPERTENSIVE  
PATIENTS. PROTOCOL 906-8"

26-JAN-89 1 INITIAL NDA - CONTINUED  
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RR 724-00093

AUTHOR: BECKER, M. ET AL  
DATE: 1-OCT-88

"REPORT OF A PLACEBO-CONTROLLED 24-HOUR BLOOD  
PRESSURE MONITORING STUDY OF ONCE AND TWICE  
DAILY ORAL DOSES OF QUINAPRIL HYDROCHLORIDE  
(CI-906) IN PATIENTS WITH MILD TO MODERATE  
HYPERTENSION (PROTOCOLS 906-250-1 THROUGH  
906-250-3)"

RR MEMO-720-02325

AUTHOR: FRNAK, G.J. ET AL  
DATE: 22-MAY-87

"TWENTY-FOUR HOUR BLOOD PRESSURE AND HEART RATE  
RESPONSES TO ONCE-DAILY QUINAPRIL HYDROCHLORIDE  
(CI-906) MEASURED BY AMBULATORY MONITORING IN  
HYPERTENSIVE PATIENTS RECEIVING OPEN-LABEL

QUINAPRIL (PROTOCOLS 906-33 AND 906-15)"

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26-JAN-89 1 INITIAL NDA - CONTINUED  
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RR 720-02331  
AUTHOR: IMBARRATO, C. ET AL  
DATE: 15-MAY-87  
"EFFECTS OF ORAL QUINAPRIL ON BLOOD PRESSURE,  
HEART RATE, AND PULMONARY FUNCTION MEASUREMENTS  
IN HEALTHY SUBJECTS (PROTOCOL 9066-232-0)"

RR 4301-00030  
AUTHORS: FRIEDRICH. T.  
SAUERMAN, W.  
DATE: 31-AUG-87  
"REPORT OF A DOUBLE-BLIND, FIXED-DOSE, PLACEBO-  
CONTROLLED, 2-WEEK STUDY OF THE EFFICACY AND  
SAFETY OF ORALLY ADMINISTERED QUINAPRIL  
HYDROCHLORIDE (CI-906) IN PATIENTS WITH MILD TO  
MODERATE HYPERTENSION UNDER EXERCISE STRESS TEST  
CONDITIONS"

26-JAN-89 1 INITIAL NDA - CONTINUED  
CONTENT:

RR X-724-00072  
AUTHOR: FRANK. G.J. ET AL  
DATE: 17-JUL-87  
"REPORT OF A SINGLE RISING-DOSE STUDY AND  
MULTIPLE-DOSE EXTENDED-TREATMENT STUDY CONDUCTED  
TO ASSESS THE SAFETY, PHARMACOLOGICAL ACTIVITY,  
AND PHARMACOKINETICS OF QUINAPRIL (CI-906)  
CAPSULES ADMINISTERED TO PATIENTS WITH  
CONGESTIVE HEART FAILURE (PROTOCOLS 906-7 AND  
906-9)"

RR 724-00082  
AUTHOR: FRANK, G.J. ET AL  
DATE: 19-NOV-87  
"A SINGLE, RISING-DOSE TRIAL TO ASSESS THE SAFETY  
AND PHARMACOLOGICAL ACTIVITY OF ORALLY  
ADMINISTERED QUINAPRIL IN PATIENTS WITH  
CONGESTIVE HEART FAILURE {PROTOCOL 906-50  
(P.239)}"

26-JAN-89 1 INITIAL NDA - CONTINUED  
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RR 724-00079  
AUTHOR: FRANK, G.J. ET AL  
DATE: 6-NOV-87  
"A SINGLE, RISING-DOSE TRIAL TO ASSESS THE SAFETY,  
PHARMACOLOGICAL ACTIVITY, AND PHARMACOKINETICS OF  
ORALLY ADMINISTERED QUINAPRIL IN PATIENTS WITH  
CONGESTIVE HEART FAILURE {PROTOCOL 906-61  
(P.254)}"

RR 724-00083  
AUTHOR: FRANK, G.J. ET AL  
DATE: 19-DEC-87  
"A 14-WEEK MULTIPLE-DOSE STUDY OF THE SAFETY

PHARMACOLOGICAL ACTIVITY, AND PHARMACOKINETICS  
OF ORALLY ADMINISTERED QUINAPRIL IN PATIENTS WITH  
CONGESTIVE HEART FAILURE {PROTOCOL 906-51  
(P.240)}"

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26-JAN-89 1 INITIAL NDA - CONTINUED  
CONTENT:

RR 724-00081  
AUTHOR: FRANK, G.J. ET AL  
DATE: 30-NOV-87  
"A 16-WEEK, MULTIPLE-DOSE STUDY OF THE SAFETY,  
PHARMACOLOGICAL ACTIVITY, AND PHARMACOKINETICS  
OF ORALLY ADMINISTERED QUINAPRIL IN PATIENTS  
WITH CONGESTIVE HEART FAILURE {PROTOCOL 906-62  
(P.255)}"

RR X-720-02147  
AUTHOR: FRANK, G.J. ET AL  
DATE: 10-AUG-88  
"REPORT OF A MULTICENTER, DOUBLE-BLIND, PLACEBO-  
CONTROLLED, SIX-WEEK, PARALLEL-GROUP, DOSE-  
RESPONSE STUDY COMPARING EFFICACY AND SAFETY OF  
PLACEBO AND 5, 10, AND 20 MG TO PATIENTS WITH  
MILD TO MODERATE HYPERTENSION (PROTOCOLS 906-12  
TO 906-22)"

26-JAN-89 1 INITIAL NDA - CONTINUED  
CONTENT:

RR X-720-02185  
AUTHOR: BOVENKERK, W.E. ET AL  
DATE: 26-AUG-88  
"REPORT OF A MULTICENTER, DOUBLE-BLIND, 12-WEEK,  
PARALLEL-GROUP STUDY COMPARING THE EFFICACY AND  
SAFETY OF ONCE-A-DAY, ORALLY ADMINISTERED  
QUINAPRIL HYDROCHLORIDE (CI-906) WITH PLACEBO;  
AND ALSO COMPARING QUINAPRIL MONOTHERAPY WITH  
CHLORTHALIDONE AND WITH CONCOMITANT QUINAPRIL  
PLUS CHLORTHALIDONE IN PATIENTS WITH MILD TO  
MODERATE HYPERTENSION (PROTOCOLS 906-30 THROUGH  
906-38, 906-40 THROUGH 906-46)"

26-JAN-89 1 INITIAL NDA - CONTINUED  
CONTENT:

RR X-720-02394  
AUTHOR: BERMAN, S.J. ET AL  
DATE: 19-NOV-88  
"AN EIGHT-WEEK, PLACEBO-CONTROLLED, DOSE-RESPONSE,  
MULTICENTER STUDY OF ORALLY ADMINISTERED  
QUINAPRIL HYDROCHLORIDE (CI-906) IN PATIENTS WITH  
MILD TO MODERATE HYPERTENSION (PROTOCOLS  
906-238-1 TO 5, 906-235-7 TO 16, AND 906-238-18  
TO 26)"

RR C-720-02327  
AUTHOR: FRANK, G.J. ET AL  
DATE: 24-AUG-87  
"REPORT OF A MULTICENTER, DOUBLE-BLIND, PLACEBO-  
CONTROLLED, 12-WEEKS STUDY COMPARING THE EFFICACY  
AND SAFETY OF TWICE-DAILY (BID) AND ONCE-DAILY  
(QD) DOSES OF ORALLY ADMINISTERED QUINAPRIL  
HYDROCHLORIDE (CI-906) IN PATIENTS WITH  
HYPERTENSION (PROTOCOLS 906-11, 906-18, 906-19, 906-20, 906-21, 906-22, 906-23, 906-24, 906-25, 906-26, 906-27, 906-28, 906-29, 906-30, 906-31, 906-32, 906-33, 906-34, 906-35, 906-36, 906-37, 906-38, 906-39, 906-40, 906-41, 906-42, 906-43, 906-44, 906-45, 906-46, 906-47, 906-48, 906-49, 906-50, 906-51, 906-52, 906-53, 906-54, 906-55, 906-56, 906-57, 906-58, 906-59, 906-60, 906-61, 906-62, 906-63, 906-64, 906-65, 906-66, 906-67, 906-68, 906-69, 906-70, 906-71, 906-72, 906-73, 906-74, 906-75, 906-76, 906-77, 906-78, 906-79, 906-80, 906-81, 906-82, 906-83, 906-84, 906-85, 906-86, 906-87, 906-88, 906-89, 906-90, 906-91, 906-92, 906-93, 906-94, 906-95, 906-96, 906-97, 906-98, 906-99, 906-100)"

AND 906-52 TO 906-59) "

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RR X-720-02346

AUTHOR: EVANS, R. ET AL

DATE: 26-AUG-88

"A MULTICENTER, DOUBLE-BLIND, PLACEBO-CONTROLLED, 12-WEEK STUDY TO COMPARE THE EFFICACY AND SAFETY OF ORALLY ADMINISTERED QUINAPRIL HYDROCHLORIDE (CI-906) TO ORALLY ADMINISTERED CAPTOPRIL IN PATIENTS WITH MILD TO MODERATE ESSENTIAL HYPERTENSION (PROTOCOL 906-114 TO 906-131, 906-133, 906-134, 906-136 TO 906-138)"

RR 720-02338

AUTHOR: FRANK, G.J. ET AL

DATE: 10-DEC-87

"A MULTICENTER, 28-WEEK, PARALLEL GROUP, RANDOMIZED, DOUBLE-BLIND, DOSE-RANGING STUDY OF QUINAPRIL (CI-906) VERSUS ENALAPRIL IN THE TREATMENT OF MILD TO MODERATE ESSENTIAL HYPERTENSION (PROTOCOL WL1-9-003-4)"

26-JAN-89 1 INITIAL NDA - CONTINUED  
CONTENT:

RR 4301-00023

AUTHORS: WOELFING, A.

LILIETHAL, J.

DATE: 11-SEP-87

"REPORT OF A MULTICENTER, DOUBLE-BLIND, 28-WEEK STUDY COMPARING THE EFFICACY AND SAFETY OF TWICE-A-DAY ORALLY ADMINISTERED QUINAPRIL HYDROCHLORIDE WITH ENALAPRIL IN PATIENTS WITH MILD TO MODERATE HYPERTENSION (CT 890-200)"

RR 720-02332

AUTHOR: FRANK, G.J. ET AL

DATE: 22-DEC-87

"OVERALL REPORT OF A MULTICENTER, DOUBLE-BLIND, 12-WEEK STUDY COMPARING THE EFFICACY AND SAFETY OF QUINAPRIL HYDROCHLORIDE (CI-906) WITH CAPTOPRIL IN THE TREATMENT OF MODERATE TO SEVERE HYPERTENSION (PROTOCOLS 906-82 TO 87, -89 TO 91, -93, -95, -96)"

26-JAN-89 1 INITIAL NDA - CONTINUED  
CONTENT:

RR 4301-00025

AUTHORS: WOELFING, A.

STERN, K.

DATE: 21-SEP-88

"REPORT OF A MULTICENTER, DOUBLE-BLIND, PARALLEL 28-WEEK STUDY COMPARING THE EFFICACY AND SAFETY OF TWICE A DAY ORALLY ADMINISTERED QUINAPRIL HYDROCHLORIDE WITH TWICE A DAY ORALLY ADMINISTERED ENALAPRIL WHEN BOTH GIVEN IN ADDITION TO ONCE A DAY CHLORTHALIDONE IN PATIENTS WITH MODERATE TO SEVERE HYPERTENSION (CT 890-170)"

RR 720-02337

AUTHOR: FRANK, G J. ET AL

DATE: 6-NOV-87

"A 28-WEEK PARALLEL GROUP DOUBLE-BLIND DOSE-  
RANGING STUDY OF QUINAPRIL (CI-906) IN THE  
TREATMENT OF MILD TO MODERATE ESSENTIAL  
HYPERTENSION (PROTOCOL 9-007)"



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26-JAN-89 1 INITIAL NDA - CONTINUED

CONTENT:

RR 720-02388

AUTHOR: BECKER, M. ET AL

DATE: 8-SEP-88

"REPORT OF THE OPEN-LABEL PHASE OF A MULTICENTER, FIXED-DOSE, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO DETERMINE EFFICACY AND SAFETY OF ORALLY ADMINISTERED QUINAPRIL HYDROCHLORIDE (CI-906) IN PATIENTS WITH MILD TO MODERATE HYPERTENSION (PROTOCOLS 906-12, 906-13, AND 906-15 TO 906-22)"

26-JAN-89 1 INITIAL NDA - CONTINUED

CONTENT:

RR 720-02334

AUTHOR: FRANK, G.J. ET AL

DATE: 25-NOV-87

"INTERIM REPORT OF THE OPEN-LABEL PHASE OF A MULTICENTER, PLACEBO-CONTROLLED STUDY TO DETERMINE THE COMPARATIVE EFFICACY AND SAFETY OF ORALLY-ADMINISTERED QUINAPRIL HYDROCHLORIDE (CI-906), CHLORTHALIDONE, AND QUINAPRIL PLUS CHLORTHALIDONE IN PATIENTS WITH MILD TO MODERATE HYPERTENSION (RR-X 720-02185) (PROTOCOLS 906-30 TO 38, -41 TO 46 )" "

26-JAN-89 1 INITIAL NDA - CONTINUED

CONTENT:

RR X-720-02318

AUTHOR: FRANK, G.J. ET AL

DATE: 19-NOV-87

"INTERIM REPORT OF THE OPEN-LABLE PHASE OF A MULTICENTER, DOUBLE-BLIND, 12-WEEK STUDY COMPARING THE EFFICACY AND SAFETY OF QUINAPRIL HYDROCHLORIDE (CI-906) WITH CAPTOPRIL IN THE TREATMENT OF MODERATE TO SEVERE HYPERTENSION (PROTOCOLS 906-82 TO 906-86, 906-89 TO 906-91, 906-93, 906-95, 906-96)"

26-JAN-89 1 INITIAL NDA - CONTINUED

CONTENT:

RR 720-02369

AUTHOR: FRANK, G.J. ET AL

DATE: 24-NOV-87

"INTERIM REPORT OF THE OPEN-LABEL PHASE OF A MULTICENTER, DOUBLE-BLIND STUDY TO COMPARE THE EFFICACY AND SAFETY OF ORALLY ADMINISTERED QUINAPRIL HYDROCHLORIDE (CI-906) TO ORALLY ADMINISTERED CAPTOPRIL IN PATIENTS WITH MILD TO MODERATE HYPERTENSION (PROTOCOLS 906-114 TO 906-131, 906-133, 906-134, 906-137, 906-138)"

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RR X-720-02392		
AUTHOR: EVANS, R. ET AL		
DATE: 11-NOV-88		
"INTERIM SUMMARY REPORT OF THE OPEN-LABEL PHASE OF FOUR MULTICENTER, DOUBLE-BLIND, PLACEBO- CONTROLLED STUDIES TO DETERMINE THE EFFICACY AND SAFETY OF ORALLY ADMINISTERED QUINAPRIL HYDROCHLORIDE (CI-906) IN PATIENTS WITH ESSENTIAL HYPERTENSION (PROTOCOLS 906-12, 906-13, 906-15 TO 906-22, 906-30 TO 906-38, 906-41 TO 906-46, 906-82 TO 906-86, 906-89 TO 906-91, 906-93, 906-95, 906-96, 906-114 TO 906-124, 906-126 TO 906-131, 906-133, 906-134, 906-137 AND 906-138)"		
26-JAN-89	1	INITIAL NDA - CONTINUED
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RR X-720-02345		
AUTHOR: FRANK, G.J. ET AL		
DATE: 25-NOV-87		
"INTERIM REPORT OF THE OPEN-LABEL PHASE OF A MULTICENTER, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO DETERMINE EFFICACY AND SAFETY OF TWICE- DAILY (BID) AND ONCE-DAILY (QD) ORAL DOSES OF QUINAPRIL HYDROCHLORIDE (CI-906) IN PATIENTS WITH HYPERTENSION (PROTOCOLS 906-11, 906-48, 906-49, AND 906-52 TO 906-59)"		
RR 764-00523		
AUTHOR: FERRY, J. ET AL		
DATE: 16-MAY-86		
"CLINICAL BIOPHARMACEUTICAL STUDY OF TWO NEW PROTOTYPE FORMULATION CAPSULES OF QUINAPRIL (CI-906) AND AN IMMEDIATE-RELEASE CAPSULE. PROTOCOL 906-81"		
26-JAN-89	1	INITIAL NDA - CONTINUED
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RR 4301-00015		
AUTHOR: BAKOVIC-ALT, R. ET AL		
DATE: 18-AUG-87		
"REPORT OF A MULTICENTER, DOUBLE-BLIND, PLACEBO CONTROLLED, 12-WEEK STUDY DETERMINING THE EFFICACY AND SAFETY OF TWICE-A-DAY, ORALLY ADMINISTERED QUINAPRIL 5 MG, 10 MG AND 20 MG IN THE TREATMENT OF CONGESTIVE HEART FAILURE (CT 891-140)"		
RR MEMO-4301-00032		
AUTHOR: BAKOVIC-ALT, R. ET AL		
DATE: 11-SEP-87		
"REPORT OF A ONE-YEAR OPEN-LABEL MULTICENTER STUDY FOLLOWING A 12-WEEK, DOUBLE-BLIND, PLACEBO CONTROLLED STUDY TO DETERMINE EFFICACY AND SAFETY OF ORALLY ADMINISTERED QUINAPRIL HYDROCHLORIDE (CI-906) IN PATIENTS WITH		

CONGESTIVE HEART FAILURE (INTERIM ANALYSIS,  
CT 891-140 FF)"

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ITEM 10: STATISTICAL SECTION		
RR X-720-02147		
AUTHOR: FRANK, G.J. ET AL		
DATE: 10-AUG-88		
"REPORT OF A MULTICENTER, DOUBLE-BLIND, PLACEBO-CONTROLLED, SIX-WEEK, PARALLEL-GROUP, DOSE-RESPONSE STUDY COMPARING EFFICACY AND SAFETY OF PLACEBO AND 5, 10, AND 20 MG QUINAPRIL HYDROCHLORIDE (CI-906) ADMINISTERED ORALLY ONCE A DAY TO PATIENTS WITH MILD TO MODERATE HYPERTENSION (PROTOCOLS 906-12 TO 906-22)"		
26-JAN-89	1	INITIAL NDA - CONTINUED
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RR X-720-02185		
AUTHOR: BOVENKERK, W.E.		
DATE: 26-AUG-88		
"REPORT OF A MULTICENTER, DOUBLE-BLIND, 12-WEEK, PARALLEL-GROUP STUDY COMPARING THE EFFICACY AND SAFETY OF ONCE-A-DAY, ORALLY ADMINISTERED QUINAPRIL HYDROCHLORIDE (CI-906) WITH PLACEBO; AND ALSO COMPARING QUINAPRIL MONOTHERAPY WITH CHLORTHALIDONE AND WITH CONCOMITANT QUINAPRIL PLUS CHLORTHALIDONE IN PATIENTS WITH MILD TO MODERATE HYPERTENSION (PROTOCOLS 906-30 THROUGH 906-38, 906-40 THROUGH 906-46)"		
26-JAN-89	1	INITIAL NDA - CONTINUED
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RR X-720-02394		
AUTHOR: BERMAN, S.J. ET AL		
DATE: 18-NOV-88		
"AN EIGHT-WEEK, PLACEBO-CONTROLLED, DOSE-RESPONSE, MULTICENTER STUDY OF ORALLY ADMINISTERED QUINAPRIL HYDROCHLORIDE (CI-906) IN PATIENTS WITH MILD TO MODERATE HYPERTENSION (PROTOCOLS 906-238-1 TO 5, 906-238-7 TO 16, 906-238-18 TO 26)"		
RR X-720-02327		
AUTHOR: FRANK, G.J. ET AL		
DATE: 24-AUG-87		
"REPORT OF A MULTICENTER, DOUBLE-BLIND, PLACEBO-CONTROLLED, 12-WEEK STUDY COMPARING THE EFFICACY AND SAFETY OF TWICE-DAILY (BID) AND ONCE-DAILY (QD) DOSES OF ORALLY ADMINISTERED QUINAPRIL HYDROCHLORIDE (CI-906) IN PATIENTS WITH HYPERTENSION (PROTOCOLS 906-11, 906-48, 906-49, AND 906-52 TO 906-59)"		

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26-JAN-89 1 INITIAL NDA - CONTINUED  
CONTENT:

RR X-720-02346

AUTHOR: EVANS, R. ET AL

DATE: 26-AUG-88

"A MULTICENTER, DOUBLE-BLIND, PLACEBO-CONTROLLED,  
12-WEEK STUDY TO COMPARE THE EFFICACY AND SAFETY  
OF ORALLY ADMINISTERED QUINAPRIL HYDROCHLORIDE  
(CI-906) TO ORALLY ADMINISTERED CAPTOPRIL IN  
PATIENTS WITH MILD TO MODERATE ESSENTIAL  
HYPERTENSION (PROTOCOL 906-114 TO 906-131,  
906-133, 906-134, 906-136 TO 906-138)"

RR 720-02338

AUTHOR: FRANK, G.J. ET AL

DATE: 10-DEC-87

"A MULTICENTER, 28-WEEK, PARALLEL GROUP,  
RANDOMIZED, DOUBLE-BLIND, DOSE-REANDING STUDY OF  
QUINAPRIL (CI-906) VERSUS ENALAPRIL IN THE  
TREATMENT OF MILD TO MODERATE ESSENTIAL  
HYPERTENSION (PTOTOCOL WLI-9-003-4)"

26-JAN-89 1 INITIAL NDA - CONTINUED  
CONTENT:

RR 4301-00023

AUTHORS: WOELFING, A.

LILIENTHAL, J.

DATE: 11-SEP-87

"REPORT OF A MULTICENTER, DOUBLE-BLIND, 28-WEEK  
STUDY COMPARING THE EFFICACY AND SAFETY OF TWICE-  
A-DAY ORALLY ADMINISTERED QUINAPRIL HYDROCHLORIDE  
WITH ENALAPRIL IN PATIENTS WITH MILD TO MODERATE  
HYPERTENSION (CT 890-200)"

RR 720-02332

AUTHOR: FRANK, G.J. ET AL

DATE: 22-DEC-87

"OVERALL REPORT OF A MULTICENTER, DOUBLE-BLIND,  
12-WEEK STUDY COMPARING THE EFFICACY AND SAFETY  
OF QUINAPRIL HYDROCHLORIDE (CI-906) WITH  
CAPTOPRIL IN THE TREATMENT OF MODERATE TO  
SEVERE HYPERTENSION (PROTOCOLS 906-82 TO 87, -89  
TO 91, -93, -95, -96)"

26-JAN-89 1 INITIAL NDA - CONTINUED  
CONTENT:

RR 4301-00025

AUTHORS: WOELFING, A.

STERN, K.

DATE: 21-SEP-88

"REPORT OF A MULTICENTER, DOUBLE-BLIND, PARALLEL  
28-WEEK STUDY COMPARING THE EFFICACY AND SAFETY  
OF TWICE A DAY ORALLY ADMINISTERED QUINAPRIL  
HYDROCHLORIDE WITH TWICE A DAY ORALLY  
ADMINISTERED ENALPRIL WHEN BOTH GIVEN IN ADDITION  
TO ONCE A DAY CHLORTHALIDONE IN PATIENTS WITH  
MODERATE TO SEVERE HYPERTENSION (CT 800-170)"

RR 720-02337

AUTHOR: FRANK, G.J. ET AL

DATE: 6-NOV-87

"A 28-WEEK PARALLEL GROUP DOUBLE-BLIND DOSE-  
RANGING STUDY OF QUINAPRIL (CI-906) IN THE  
TREATMENT OF MILD TO MODERATE ESSENTIAL  
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ITEM 12: CASE REPORT FORMS		
ITEM 13: PATENT AND MARKET EXCLUSIVITY INFORMATION.		
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10-MAY-89		FDA CONTACT MEMO
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MEMO RE: DRUG EVALUATION		
CONTACT PERSON: CUNNINGHAM, DONNA		
TELEPHONE CONVERSATION RE: THE SUBMISSION OF		
SAMPLES FOR BOTH DRUG SUBSTANCE AND DRUG PRODUCT		
ANALYTIC METHODS TO DETROIT AND ST. LOUIS.		
11-MAY-89		FDA CONTACT MEMO
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MEMO RE: HPLC AND PACKAGING.		
CONTACT PERSON: CUNNINGHAM, DONNA		
TELEPHONE CONVERSATION RE: THE HPLC ANALYTIC		
METHOD FOR DIASTERIOMERIC IMPURITIES IMPROVEMENT		
AND TO DISCUSS INCORPORATING THE IMPROVED METHOD		
INTO THE PACKAGES.		
18-MAY-89		EXPORT APPLICATION
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DRUG TO: FRANCE		
23-MAY-89		LETTER RE: METHOD VALIDATION
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LETTER TO: SCHNEIDER, LEWIS F. (DETROIT, MI)		
DREW, HENRY (ST. LOUIS, MO)		
RE: METHOD VALIDATION SAMPLES.		
23-MAY-89	2	MINUTES OF FDA MEETING
CONTENT:		
DATE: 17-MAY-89		
FDA MEETING TO DISCUSS THIS NDA AND THE FOLLOWING:		
1) COPY OF THE STUDY REPORTS.		
2) LETTER SENT TO DR. BASIL FRIEDMAN.		

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25-MAY-89 LETTER FROM FDA RE: EXPORT APPLICATION  
CONTENT:

LETTER FROM: COOPER, MARY F.  
RE: REQUEST ADDITIONAL INFORMATION REGARDING THE  
EXPORT APPLICATION TO FRANCE.  
CROSS REFERENCE: DATE - 18-MAY-89

26-MAY-89 SAFETY UPDATE  
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ITEM 1: SUBMISSION INDEX.  
ITEM 5: NONCLINICAL PHARMACOLOGY AND TOXICOLOGY.

RR 745-01450  
AUTHOR: GOUGH, A.W. ET AL  
DATE: 8-MAY-89  
"HISTOPATHOLOGIC REVIEW OF KIDNEYS FROM RODENT  
CHRONIC TOXICITY STUDIES AND TUMOR BIOASSAYS  
WITH CI-906"

RR 745-01384  
AUTHOR: MACDONALD, J.R. ET AL  
DATE: 9-MAY-89  
"EFFECTS OF CI-906 ADMINISTERED ORALLY FOR FOUR  
WEEKS ON RENAL FUNCTIONAL PARAMETERS IN MALE  
RATS"

26-MAY-89 SAFETY UPDATE - CONTINUED  
CONTENT:

RR 745-01350  
AUTHOR: DETHLOFF, L.A. ET AL  
DATE: 10-MAY-89  
"THE EFFECTS OF CI-906 (QUINAPRIL) ON RENAL  
FUNCTION AND RENAL HEMODYNAMICS IN RATS"

RR 745-01430  
AUTHOR: SUSICK, R.L. ET AL  
DATE: 9-MAY-89  
"RENAL FUNCTION AND HEMODYNAMICS IN DOGS AFTER  
THIRTEEN-WEEK ORAL ADMINISTRATION OF CI-906"

RR 745-01408  
AUTHOR: HENEK, J.W.  
DATE: 12-MAY-89  
"TWO-WEEK ORAL TOXICITY STUDY OF CI-906 IN FEMALE  
RABBITS"

26-MAY-89 SAFETY UPDATE - CONTINUED  
CONTENT:

RR 745-01412  
AUTHOR: PETRERE, J.A. ET AL  
DATE: 9-MAY-89  
"MODIFIED PERINATAL-POSTNATAL STUDY IN RATS WITH  
CI-906"

RR 745-01421



AUTHOR: GOUGH, A.W. ET AL  
DATE: 9-MAY-89  
"IN VITRO CHROMOSOMAL ABERRATION ASSAY OF CI-906  
IN V79 CHINESE HAMSTER LUNG CELLS"

RR 745-01330  
AUTHOR: ULLOA, H.M. ET AL  
DATE: 9-MAY-89  
"DERMAL SENSITIZATION STUDY OF CI-906 (QUINAPRIL)  
IN GUINEA PIGS (MAXIMIZATION TEST)"

ITEM 12: CASE REPORT FORMS.

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DOC DATE	SER/SUPPL NO	TITLE
02-JUN-89	3	LETTER RE: METHOD VALIDATION
CONTENT:		LETTER TO: LIPICKY, RAYMOND J., M.D. RE: REVISED TEST METHODS PER THE TELEPHONE CONVERSATION WITH DONNA CUNNINGHAM. CROSS REFERENCE: DATE - 11-MAY-89
06-JUN-89		LETTER RE: SAFETY UPDATE
CONTENT:		LETTER TO: FRIEDMAN, BASIL RE: PROVIDED COPY OF CLINICAL DATA IN SUPPORT OF THE SAFETY UPDATE.
06-JUN-89		MEMO RE: FDA MEETING
CONTENT:		MEMO RE: NDA STATUS AS STATED AT 5-JUN-89 FDA MEETING.
08-JUN-89		FDA CONTACT MEMO
CONTENT:		MEMO RE: PR. 906-3 CONTACT PERSON: FRIEDMAN, BASIL TELEPHONE CONVERSATION RE: CI-906 ADMINISTRATION SCHEDULE FOR PATIENT #2.
08-JUN-89		LETTER RE: DRUG ADMINISTRATION
CONTENT:		LETTER TO: FRIEDMAN, BASIL PR. 906-3 RE: PROVIDE CORRECT SCHEDULE.
16-JUN-89		LETTER FROM FDA RE: MANUFACTURING AND CONTROLS
CONTENT:		LETTER FROM: LIPICKY, RAYMOND J., M.D. RE: REVIEW HAS BEEN COMPLETED REGARDING THE MANUFACTURING AND CONTROLS PORTION OF THE NDA WITH 12 RECOMMENDATION AND REQUESTS.
22-JUN-89		FDA CONTACT MEMO
CONTENT:		MEMO RE: DIASTOLIC BLOOD PRESSURE CONTACT PERSON: FRIEDMAN, BASIL TELEPHONE CONVERSATION RE: THE SPECIFIC OF DIASTOLIC BLOOD PRESSURE.

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22-JUN-89 FDA CONTACT MEMO  
CONTENT:

MEMO RE: QUINAPRIL, QUINAPRIL/DILTIAZEM AND  
PIRMENOL.

CONTACT PERSON: LIPICKY, RAYMOND J.  
VERBAL CONVERSATION RE: AFTER 15-JUN-89 MEETING  
ON PROCAN SR BID THE FOLLOWING ISSUE WAS  
ADDRESSED:

- 1) DEVELOPMENT OF AN ACE INHIBITOR/CALCIUM CHANNEL
- 2) NDAS ON ACE INHIBITORS WOULD NOT BE BROUGHT  
BEFORE THE ADVISORY COMMITTEE.

26-JUN-89 FDA CONTACT MEMO  
CONTENT:

MEMO RE: EXPORT APPLICATION.  
CONTACT PERSON: BECK, ELLIOTT  
TELEPHONE CONVERSATION RE: ACUITEL WILL ONLY BE  
MARKETED IN BLISTER PACKS IN FRANCE.

28-JUN-89 LETTER TO: EXPORT APPLICATION  
CONTENT:

LETTER TO: COOPER, MARY  
RE: RESUBMISSION OF EXPORT APPLICATION TO FRANCE.

18-JUL-89 FDA CONTACT MEMO  
CONTENT:

MEMO RE: PR. 906-238 AND RR 720-02394  
CONTACT PERSON: FRIEDMAN, BASIL  
TELEPHONE CONVERSATION RE: SEVERAL QUESTIONS  
REGARDING THE STUDY.

18-JUL-89 LETTER RE: RESPONSE TO VERBAL REQUEST FOR INFORMATION  
CONTENT:

LETTER TO: FRIEDMAN, BASIL  
RE: RESPONSE TO TELEPHONE CONVERSATION REGARDING  
A COPY OF VOLUME 106 OF THE NDA TO REPLACE  
VOLUME MISSING PAGES.

20-JUL-89 4 LETTER RE: RESPONSE TO REQUEST FOR INFORMATION  
CONTENT:

LETTER TO: LIPICKY, RAYMOND J., M.D.  
RE: RESPONSE TO DR. BASIL FRIEDMAN REQUEST FOR  
INFORMATION. (THREE TELEPHONE REPORTS)

31-JUL-89 FDA CONTACT MEMO  
CONTENT:

MEMO RE: EXPORT APPLICATION  
CONTACT PERSON: COOPER, MARY F.  
TELEPHONE CONVERSATION RE: 28-JUL-89 OF HOW TO  
COORDINATE INCLUSION OF ITALY AND UNITED KINGDOM  
APPROVALS INTO OUR EXPORT APPLICATION.

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01-AUG-89 CONTENT:	4	LETTER RE: RESPONSE TO REQUEST FOR INFORMATION  LETTER TO: LIPICKY, RAYMOND J., M.D. RE: RESPONSE TO 16-JUN-89 WRITTEN REQUEST FOR ADDITIONAL INFORMATION REGARDING CHEMISTRY, MANUFACTURING AND CONTROL.
15-AUG-89 CONTENT:		FDA CONTACT MEMO  MEMO RE: 9-003-3 CONTACT PERSON: FRIEDMAN, BASIL TELEPHONE CONVERSATION RE: REQUEST EXPLANATION OF APPARENTLY LOW NUMBER OF EVALUABLE PATIENTS.
15-AUG-89 CONTENT:		FDA CONTACT MEMO  MEMO RE: 9-003-3 CONTACT PERSON: FRIEDMAN, BASIL TELEPHONE CONVERSATION RE: REQUEST ADDITIONAL INFORMATION REGARDING THE STUDY.
16-AUG-89 CONTENT:		FDA CONTACT MEMO  MEMO RE: 9-003-3 CONTACT PERSON: FRIEDMAN, BASIL TELEPHONE CONVERSATION RE: REQUEST ADDITIONAL INFORMATION REGARDING EVALUABLE PATIENTS IN STUDY.
24-AUG-89 CONTENT:		LETTER RE: RESPONSE TO REQUEST FOR INFORMATION  LETTER TO: FRIEDMAN, BASIL PR. 9-003-3 RE: RESPONSE TO 15-AUG-89 AND 16-AUG-89 VERBAL REQUEST FOR ADDITIONAL INFORMATION.
05-SEP-89 CONTENT:		LETTER FROM FDA RE: EXPORT APPROVAL  LETTER FROM: MICHELS, DANIEL L. RE: APPROVAL TO EXPORT QUINAPRIL HYDROCHLORIDE (IN BULK FORM: ACUITEL) PACKAGING IS IN BOTTLES OF 5 MG AND 20 MG TABLETS AND UNIT DOSE IN 5 MG AND 20 MG BLISTER PACKAGES TO FRANCE.

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06-SEP-89 LETTER RE: RESPONSE TO REQUEST FOR INFORMATION  
CONTENT:

LETTER TO: FRIEDMAN, BASIL

PR. 906-12

RE: RESPONSE TO REQUEST FOR ADDITIONAL INFORMATION  
REGARDING THE STUDY AS FOLLOWS:

- 1) HOW ARE PATIENTS WHO RECEIVE BETA BLOCKERS OR  
CALCIUM CHANNEL BLOCKERS ASSIGNED TO THE  
MONOTHERAPY AND MONOTHERAPY PLUS DIURETIC  
CATAGORIES?
- 2) IDENTIFY INFORMATION IN THE NDA ON PATIENTS  
WITH RENAL INSUFFICIENCY.

11-SEP-89 MEMO RE: STATUS OF METHOD VALIDATION  
CONTENT:

MEMO TO: DREW, HENRY (FDA, ST LOUIS)

RE: PER TELEPHONE CONVERSATION, THE ANALYSIS  
WAS COMPLETED AND THE REPORT WAS FORWARDED  
21-AUG-89.

12-SEP-89 LETTER RE: RESPONSE TO REQUEST FOR INFORMATION  
CONTENT:

LETTER TO: FRIEDMAN, BASIL

PR. 906-12

RE: RESPONSE TO QUESTIONS REGARDING THE OPEN-LABEL  
EXTENSION AND THE LOCATION OF INFORMATION ON  
PATIENTS WITH RENAL INSUFFICIENCY.

13-SEP-89 5 LETTER RE: AMENDMENT TO NDA  
CONTENT:

LETTER TO: LIPICKY, RAYMOND J.

RE: TO PROVIDE ADDITIONAL DRUG PRODUCT  
MANUFACTURING SITE AND ADDITIONAL PACKAGING  
SITE ADDRESSES AND FACILITIES.

15-SEP-89 FDA CONTACT MEMO  
CONTENT:

MEMO RE: REVIEW OF THE CLINICAL DATA IN NDA  
CONTACT PERSON: FRIEDMAN, BASIL  
TELEPHONE CONVERSATION RE: HAVE COMPLETED REVIEW  
OF EFFICACY AND SAFETY.

18-SEP-89 FDA CONTACT MEMO  
CONTENT:

MEMO RE: PIVOTAL EFFICACY STUDIES

CONTACT PERSON: SEGAL, DORALIE

TELEPHONE CONVERSATION RE: DR. FRIEDMAN'S VERBAL  
REQUEST TO HER FOR ADDITIONAL INFORMATION  
REGARDING PRS. 906-12, 30 AND 238 AS FOLLOWS:

- 1) LIST OF INVESTIGATORS.
- 2) PATIENTS NUMBER UNDER EACH INVESTIGATOR.
- 3) NUMBER OF PATIENTS COMPLETED UNDER EACH  
INVESTIGATOR.

4) NUMBER USED FOR EFFICACY ANALYSIS

- 5) COPY OF THE PROTOCOL.
- 6) BLANK CRF'S.

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DOC DATE	SER/SUPPL NO	TITLE
18-SEP-89		FDA CONTACT MEMO
CONTENT:		MEMO RE: RANDOMIZATION CODES AND PIVOTAL PROOF OF EFFICACY CONTACT PERSON: FRIEDMAN, BASIL TELEPHONE CONVERSATION RE: REQUEST RULES FOR THE FOLLOWING: 1) BREAKING DOUBLE-BLIND CODES. 2) PROOF OF EFFICACY TO COMPLETE OVERALL SUMMARY.
21-SEP-89		LETTER RE: RESPONSE TO REQUEST FOR INFORMATION
CONTENT:		LETTER TO: FRIEDMAN, BASIL PRS. 906-82, 238, 9-003-3, 4 AND 9-008-1 RE: RESPONSE TO REQUEST TO DESCRIBE PROCEDURES FOR CODE BREAKING IN THE BLINDED STUDIES.
22-SEP-89		MEMO RE: STATUS OF METHOD VALIDATION
CONTENT:		MEMO TO: SCHNEIDER, FELIX (FDA, DETROIT) RE: THE ANALYSIS WAS COMPLETED AND THE REPORT WILL BE SENT 25-SEP-89.
03-OCT-89		LETTER RE: RESPONSE TO REQUEST FOR INFORMATION
CONTENT:		LETTER TO: SEGAL, DORALIE PRS. 906-12, 30 AND 238 RE: RESPONSE TO 18-SEP-89 REQUEST FOR INFORMATION REGARDING THE FOLLOWING: 1) LIST OF PRINCIPLE INVESTIGATORS. 2) PATIENT INFORMATION. 3) COPY OF PROTOCOL. 4) BLANK CASE REPORT FORMS.
03-OCT-89	6	LETTER RE: VERBAL REQUEST FOR INFORMATION
CONTENT:		LETTER TO: LIPICKY, RAYMOND J., M.D. PRS. 906-12, 30 AND 238 RE: 18-SEP-89 TELEPHONE CONVERSATION WITH DORALIE SEGAL REQUESTING THE FOLLOWING ON PIVOTAL STUDIES: 1) LIST OF PRINCIPAL INVESTIGATORS. 2) PATIENT INFORMATION. 3) COPY OF PROTOCOLS. 4) BLANK CASE REPORT FORMS.

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13-OCT-89 MEMO RE: FDA STUDY SITES AUDITS  
CONTENT: MEMO RE: TELEPHONE CONVERSATION WITH MS. SEGAL  
REGARDING THE VERIFICATION OF RECEIPT OF  
INVESTIGATOR AND PATIENT INFORMATION  
SENT 5-OCT-89 FOR FDA AUDIT.

19-OCT-89 2 EXPORT APPLICATION  
CONTENT: END-0058  
ITALY  
GREAT BRITAIN

15-NOV-89 LETTER FROM FDA RE: EXPORT APPROVAL  
CONTENT: LETTER FROM: MICHELS, DANIEL  
RE: APPROVAL TO EXPORT QUINAPRIL TO ITALY AND  
THE UNITED KINGDOM.

06-DEC-89 3 EXPORT APPLICATION  
CONTENT: END-0058  
ITALY  
UNITED KINGDOM

21-DEC-89 LETTER FROM FDA RE: EXPORT APPROVAL  
CONTENT: LETTER FROM: MICHELS, DANIEL L.  
RE: APPROVED THE EXPORTATION OF QUINAPRIL  
HYDROCHLORIDE BULK FORM TO ITALY AND  
THE UNITED KINGDOM.

02-JAN-90 FDA CONTACT MEMO  
CONTENT: MEMO RE: SAFETY REPORT  
CONTACT PERSON: BONGIOVANNI, KATHLEEN  
TELEPHONE CONVERSATION RE: CONFIRMING THE RECEIPT  
OF THE 10-DAY SAFETY REPORT.

02-JAN-90 FDA CONTACT MEMO  
CONTENT: MEMO RE: GENERAL INFORMATION  
CONTACT PERSON: FRIEDMAN, BASIL  
TELEPHONE CONVERSATION RE: INFORMED HIM THAT  
DR. VILLAUME HAS LEFT THE COMPANY AND INQUIRED  
HOW DR. LIPICKY'S REVIEW WAS GOING.



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03-JAN-90 LETTER RE: INTERNATIONAL DRUG OBJECTION  
CONTENT:

LETTER TO: AHLGREN, KARIN  
RE: SWEDEN HAS OBJECTED TO QUINAPRIL IN THE  
COUNTRY. RESEARCH REPORTS WERE PROVIDED FOR  
THE RESPONSES OF THE OVERALL ASSESSMENT FROM  
THE SWEDISH REGULATORY AUTHORITY.

05-JAN-90 LETTER RE: RESPONSE TO REQUEST FOR INFORMATION  
CONTENT:

LETTER TO: AHLGREN, KARIN  
RE: PROVIDED RESEARCH REPORTS THAT WERE MISSING  
FROM OTHER INFORMATION SECTION IN THE MAA.

10-JAN-90 LETTER RE: GENERAL INFORMATION  
CONTENT:

LETTER TO: AHLGREN, KARIN  
RE: DRAFT COPY ON THE EUROPEAN SYMPOSIUM ON  
BIOAVAILABILITY ALONG WITH RR X-745-01381.

12-JAN-90 LETTER RE: RESPONSE TO REQUEST FOR INFORMATION  
CONTENT:

LETTER TO: AHLGREN, KARIN  
RE: RESPONSE TO CONCERNS REGARDING SWEDISH DRA  
QUESTIONS.

19-JAN-90 FDA CONTACT MEMO  
CONTENT:

MEMO RE: NDA STATUS  
CONTACT PERSON: BONGIOVANNI, KATHLEEN  
TELEPHONE CONVERSATION RE:  
1) DR. TRAN IS THE BIOPHARMACEUTIC REVIEWER.  
2) THE CLINICAL DATA HAS NOT BEEN REVIEWED YET.  
3) THE PRECLINICAL REVIEW IS UNDERWAY.

09-FEB-90 FDA CONTACT MEMO  
CONTENT:

MEMO RE: TROUGH BLOOD PRESSURE MEASUREMENT  
CONTACT PERSON: FRIEDMAN, BASIL  
TELEPHONE CONVERSATION RE: CONCERNS ABOUT THE  
TROUGH BLOOD PRESSURE MEASUREMENT IN BID  
STUDY 9-003-3.

13-FEB-90 FDA CONTACT MEMO  
CONTENT:

MEMO RE: DR. FRIEDMAN'S REQUEST INFORMATION  
CONTACT PERSON: BONGIOVANNI, KATHLEEN  
TELEPHONE CONVERSATION RE: REQUEST ADDITIONAL  
INFORMATION REGARDING THE RECENT CLINICAL STUDY  
REPORTS SUBMITTED TO THE QUINAPRIL IND.

CONFERENCE CALL RE: UPDATING OUR EFFICACY DATA  
WITH NEW DATA

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21-FEB-90 LETTER RE: GENERAL INFORMATION  
CONTENT:

LETTER TO: TSUI, D.  
RE: PROVIDED PROTOCOL REGARDING THE  
BIOAVAILABILITY OF QUINAPRILAT FOLLOWING  
ORAL ADMINISTRATION OF QUINAPRIL.

14-MAR-90 LETTER RE: VERBAL REQUEST FOR MEETING  
CONTENT:

LETTER TO: FRIEDMAN, BASIL  
RE: TELEPHONE CONVERSATION ON 12-MAR-90 REQUESTING  
MEETING TO REVIEW TIME WINDOW FOR TROUGH  
BLOOD PRESSURE MEASUREMENTS. MEETING  
SCHEDULED 20-MAR-90.

26-MAR-90 LETTER RE: RESPONSE TO REQUEST FOR INFORMATION  
CONTENT:

LETTER TO: TSUI, D.  
RE: RESPONSE TO ISSUES RAISED BY AUSTRALIAN DRA  
ON QUINAPRIL APPLICATION.

29-MAR-90 7 MINUTES OF FDA MEETING  
CONTENT:

DATE: 20-MAR-90  
MEETING WITH DR. FRIEDMAN RE: TO REVIEW THE TIME  
WINDOW FOR TROUGH BLOOD PRESSURE MEASUREMENTS.

29-MAR-90 8 LETTER RE: RESPONSE TO VERBAL REQUEST FOR INFORMATION  
CONTENT:

LETTER TO: LIPICKY, RAYMOND J., M.D.  
RE: RESPONSE TO 19-JAN-90 AND 14-MAR-90  
TELEPHONE CONVERSATION REGARDING MOUSE  
AND RAT CARCINOGENICITY BIOASSAYS FOR  
USE BY DR. VANARSDEL.

04-APR-90 MEMO RE: TRIP REPORT  
CONTENT:

MEMO RE: TRIP REPORT REGARDING 3-MAR-90 MEETING  
WITH FDA.

06-APR-90 MEMO RE: NDA REVIEW  
CONTENT:

MEMO RE: NDA BIOPHARMACEUTICS REVIEW OF THE NDA.

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06-APR-90 CONTENT:	10	LETTER RE: RESPONSE TO REQUEST FOR INFORMATION  LETTER TO: LIPICKY, RAYMOND J., M.D. RE: RESPONSE TO SEVERAL REQUESTS FOR INFORMATION.
17-APR-90 CONTENT:	9	LETTER RE: CHEMISTRY, MANUFACTURING AND CONTROLS  LETTER TO: LIPICKY, RAYMOND J., M.D. RE: UPDATED CHEMISTRY, MANUFACTURING AND CONTROLS DATA.
20-APR-90 CONTENT:		LETTER RE: MEETING CONFIRMATION  LETTER TO: WOLTER, ROBERT RE: CONFIRMATION OF MEETING TO BE HELD 7-MAY-90 TO DISCUSS DESIGNATION OF STARTING MATERIAL IN THE SYNTHESIS OF QUINAPRIL HYDROCHLORIDE.
26-APR-90 CONTENT:		MEMO RE: FDA VISIT  MEMO RE: VISIT WITH BONGIOVANNI, KATHLEEN REGARDING THE FOLLOWING: 1) CONFIRMATION OF 7-MAY-90 MEETING. 2) FINAL SAFETY UPDATE IS PLANNED FOR COMPLETION IN JUNE WITH SUBMISSION IN JULY.
10-MAY-90 CONTENT:		LETTER FROM FDA RE: MINUTES OF FDA MEETING  LETTER FROM: MORGENSTERN, NATALIA A. DATE: 28-NOV-89 FDA MEETING RE: PRE-NDA MEETING FOR QUINAPRIL/HCTZ COMBINATION PRODUCT.
15-MAY-90 CONTENT:		FDA CONTACT MEMO  MEMO RE: CHEMISTRY CONTACT PERSON: WOLTERS, ROBERT FDA MEETING RE: DISCUSSION WITH CHEMISTRY REVIEWER CONCERNING QUINAPRIL.
18-MAY-90 CONTENT:		FDA CONTACT MEMO  MEMO RE: NDA AND SBA CONTACT PERSON: RESNICK, CHARLES TELEPHONE CONVERSATION RE: FOLLOW-UP TO MEETING REQUEST ON 7-MAY-90 REGARDING CONFLICTING REPORTS FROM THE AGENCY CONCERNING SCALE-UP LOT REQUIREMENTS FOR NCE NDAS.

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18-MAY-90		FDA CONTACT MEMO
CONTENT:		MEMO RE: FOLLOW-UP ON MEETING CONTACT PERSON: WOLTERS, R. TELEPHONE CONVERSATION RE: FOLLOW-UP TO 7-MAY-90 MEETING.
21-MAY-90		FDA CONTACT MEMO
CONTENT:		MEMO RE: NDA REVIEW CONTACT PERSON: HUANG, MEI-YING NG, TIE-HUA CHEN, SHAW FDA MEETING RE: STATUS OF PENDING NDA REVIEWS.
01-JUN-90		FDA CONTACT MEMO
CONTENT:		MEMO RE: FOLLOW-UP ON SUBMISSION CONTACT PERSON: BONGIOVANNI, KATHLEEN TELEPHONE CONVERSATION RE: FOLLOW-UP ON REQUEST FOR INFORMATION REGARDING 18-MAY-90 SUBMISSION.
04-JUN-90		FDA CONTACT MEMO
CONTENT:		MEMO RE: FOLLOW-UP TO CONVERSATION CONTACT PERSON: GRAHAM, CHERYL FDA MEETING RE: FOLLOW-UP TO 1-JUN-90 CONVERSATION WITH KATHLEEN BONGIOVANNI.
11-JUN-90		FDA CONTACT MEMO
CONTENT:		MEMO RE: HOLD ON MEETING CONTACT PERSON: BONGIOVANNI, KATHLEEN TELEPHONE CONVERSATION RE: HER MEETING WITH DRS. CHEN, GRAHAM AND CHEN WILL WAIT TILL THE COMPLETION OF ALL REVIEWS.
13-JUN-90		MEMO RE: SUMMARY OF NDA AND MAA
CONTENT:		MEMO RE: CLINICAL SUMMARIES FOR QUINAPRIL NDA AND TACRINE MAA.
18-JUN-90		FDA CONTACT MEMO
CONTENT:		MEMO RE: FDA FIELD INSPECTION OF PIVOTAL STUDY SITES. CONTACT PERSON: DR. ELHAGE TELEPHONE CONVERSATION RE: MS. DORALIE SEGAL HAS LEFT THE AGENCY AND THE FDA INSPECTION FOR SITES 906-12 AND 30 HAS BEEN DELAYED.

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25-JUN-90		FDA CONTACT MEMO
CONTENT:		MEMO RE: REQUEST FDA MEETING CONTACT PERSON: VANARSDALE, W TELEPHONE CONVERSATION RE: REQUEST FDA MEETING ON 27-JUN-90.
28-JUN-90		MEMO RE: CSA
CONTENT:		MEMO RE: CSA FOR PR. 906-345. PROVIDED ADDITIONAL INFORMATION IN SUPPORT OF CSA FOR QUINAPRIL/DILITAZE.
29-JUN-90		FDA CONTACT MEMO
CONTENT:		MEMO RE: FOLLOW-UP TO VERBAL REQUEST CONTACT PERSON: RESNICK, CHARLES TELEPHONE CONVERSATION RE: REQUEST ADDITIONAL PHARMACOLOGY REPORTS AND DRAFT SBA.
06-JUL-90		FDA CONTACT MEMO
CONTENT:		MEMO RE: STATUS OF NDA REVIEWS CONTACT PERSON: BONGIOVANNI, KATHLEEN TELEPHONE CONVERSATION RE: REQUEST STATUS OF NDA REVIEW. SHE REQUESTED A DESK COPY OF THE REVISED LABELING.
06-JUL-90		FDA CONTACT MEMO
CONTENT:		MEMO RE: STATUS OF REVIEW CONTACT PERSON: LIPICKY, RAYMOND J. TELEPHONE CONVERSATION RE: QUESTIONS REGARDING QUINAPRIL REVIEW STATUS. SBA FORMAT MEETING SCHEDULED FOR 10-JUL-90.
10-JUL-90		LETTER FROM FDA RE: REQUEST INFORMATION
CONTENT:		LETTER FROM: MORGENSTERN, NATALIA A. RE: QUESTIONS RAISED FROM REVIEWING SUBMISSION OF 26-JAN-89.
13-JUL-90		FDA CONTACT MEMO
CONTENT:		MEMO RE: CLINICAL INSPECTION AND SBA CONTACT PERSON: BONGIOVANNI, KATHLEEN FDA MEETING TO FOLLOW-UP THE 10-JUL-90 DISCUSSION REGARDING CLINICAL INSPECTION AND SBA.

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13-JUL-90 FDA CONTACT MEMO

CONTENT:

MEMO RE: NDAS  
CONTACT PERSON: WOLTERS, ROBERT  
FDA MEETING TO DISCUSS QUESTIONS ON PENDING  
QUINAPRIL NDA AND FUTURE Q/HCTZ NDA EA.

13-JUL-90 FDA CONTACT MEMO

CONTENT:

MEMO RE: SBA  
CONTACT PERSON: RESNICK, CHARLES  
FDA MEETING TO DISCUSS THE FORMAT OF SBA FOR  
PRECLINICAL SECTION.

18-JUL-90 FDA CONTACT MEMO

CONTENT:

MEMO RE: REQUEST INFORMATION  
CONTACT PERSON: BONGIOVANNI, KATHLEEN  
TELEPHONE CONVERSATION RE: REQUEST PROTOCOL  
NUMBERS FOR INVESTIGATORS TO BE AUDITED.

20-JUL-90 FDA CONTACT MEMO

CONTENT:

MEMO RE: DRAFT SBA  
CONTACT PERSON: RESNICK,  
TELEPHONE CONVERSATION RE: REQUEST HIS OPINION  
ON THE DRAFT SBA FORMAT AND HIS LISTED SPECIFIC  
COMMENTS.

24-JUL-90 MINUTES OF FDA MEETING

CONTENT:

DATE: 10-JUL-90  
FDA MEETING RE: TO DISCUSS THE SBA.

25-JUL-90 11 SAFETY UPDATE

CONTENT:

VOLUMES=34

25-JUL-90 12 LETTER RE: PACKAGE INSERT

CONTENT:

LETTER TO: LIPICKY, RAYMOND J.  
VOLUMES=7  
RE: PACKAGE INSERT.

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31-JUL-90 FDA CONTACT MEMO  
CONTENT:

MEMO RE: CONFIRMATION OF SAFETY UPDATE  
CONTACT PERSON: BONGIOVANNI, KATHLEEN  
TELEPHONE CONVERSATION RE: CONFIRMATION OF RECEIPT  
OF SAFETY UPDATE AND REVISED PACKAGE INSERT.

06-AUG-90 FDA CONTACT MEMO  
CONTENT:

MEMO RE: REQUEST FOR INFORMATION  
CONTACT PERSON: SAMARA, DR.  
TELEPHONE CONVERSATION RE: QUESTIONS DURING  
NDA REVIEW.

07-AUG-90 FDA CONTACT MEMO  
CONTENT:

MEMO RE: FOLLOW-UP  
CONTACT PERSON: SAMARA, DR.  
TELEPHONE CONVERSATION RE: FOLLOW-UP TO 6-AUG-90  
REQUEST FOR ADDITIONAL INFORMATION.

08-AUG-90 FDA CONTACT MEMO  
CONTENT:

MEMO RE: SAFETY UPDATE  
CONTACT PERSON: FREIDMAN, BASIL  
TELEPHONE CONVERSATION RE: SECOND SAFETY UPDATE.

09-AUG-90

13-AUG-90 ANNUAL REPORT  
CONTENT:

END-0058  
END-0058A01  
END-0058A02

14-AUG-90 14 LETTER RE: RESPONSE TO REQUEST FOR INFORMATION  
CONTENT:  
LETTER TO: LIPICKY, RAYMOND J.  
RE: RESPONSE TO BIOPHARMACEUTICS QUESTIONS ON  
QUINAPRIL NDA.

17-AUG-90 FDA CONTACT MEMO  
CONTENT:

MEMO RE: FOLLOW-UP TO SBA  
CONTACT PERSON: BONGIOVANNI, KATHLEEN  
TELEPHONE CONVERSATION RE: FOLLOW-UP TO  
SENDING OF DRAFT FIGURES FOR SBA.

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21-AUG-90 FDA CONTACT MEMO  
CONTENT:

MEMO RE: STATUS  
CONTACT PERSON: BONGIOVANNI, KATHLEEN  
MEETING WITH FDA RE: PENDING NDA. THE FOLLOWING  
WAS DISCUSSED:  
1) THE BIOPHARM. IS ACTIVELY BEING REVIEWED.  
2) THE BIOSTAT. HAS BEGUN HIS REVIEW.  
3) DR. FRIEDMAN HAS COMPLETED HIS REVIEW OF THE  
SAFETY UPDATE AND THE SECONDARY REVIEW SHALL  
BEGIN.  
4) WE ARE WORKING ON BOTH THE PRECLINICAL AND  
CLINICAL SBAS.

21-AUG-90 FDA CONTACT MEMO  
CONTENT:

MEMO RE: FOLLOW-UP ON REQUEST  
CONTACT PERSON: SAMARA, DR.  
MEETING WITH FDA RE: HIS REVIEW OF THE QUINAPRIL  
NDA BIOPHARM. SECTION.

22-AUG-90 FDA CONTACT MEMO  
CONTENT:

MEMO RE: SBA  
CONTACT PERSON: BONGIOVANNI, KATHLEEN  
TELEPHONE CONVERSATION RE: REVIEW OF DRAFT  
FIGURES FOR QUINAPRIL SBA.

31-AUG-90 FDA CONTACT MEMO  
CONTENT:

MEMO RE: STATUS REPORT  
CONTACT PERSON: CUNNINGHAM, DANUTE  
TELEPHONE CONVERSATION RE: STATUS OF REQUEST  
FOR INSPECTION OF MANUFACTURING SITES.

31-AUG-90 FDA CONTACT MEMO  
CONTENT:

MEMO RE: MANUFACTURING STATUS  
CONTACT PERSON: CUNNINGHAM, DANUTE  
TELEPHONE CONVERSATION RE: STATUS OF REQUEST FOR  
INSPECTION OF MANUFACTURING SITES.

21-SEP-90 15 LETTER RE: SUMMAY BASIS OF APPROVAL  
CONTENT:

LETTER TO: LIPICKY, RAYMOND J.  
RE: PROVIDED A DRAFT SUMMARY BASIS OF APPROVAL FOR  
FDA'S REVIEW AND COMMENTS



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27-SEP-90 FDA CONTACT MEMO  
CONTENT:

MEMO RE: SBA RECEIPT CONFIRMATION  
CONTACT PERSON: RESNICK, CHARLES  
TELEPHONE CONVERSATION RE: REQUEST CONFIRMATION  
OF RECEIPT OF SBA AND CHECK STATUS OF NDA REVIEW.  
SBA WAS NOT RECEIVED, ANOTHER COPY OF THE SBA  
WAS SENT.

27-SEP-90 FDA CONTACT MEMO  
CONTENT:

MEMO RE: MEETING REQUEST  
CONTACT PERSON: BONGIOVANNI, KATHLEEN  
TELEPHONE CONVERSATION RE: REQUEST MEETING TO  
ASSESS THE REALISTIC PROBABILITY FOR A 1990  
APPROVAL FOR QUINAPRIL.

28-SEP-90 FDA CONTACT MEMO  
CONTENT:

MEMO RE: FOLLOW-UP TO MEETING REQUEST  
CONTACT PERSON: BONGIOVANNI, KATHLEEN  
TELEPHONE CALL RE: OFFERED 12-OCT-90, 3 PM FOR  
MEETING TO ASSESS THE REALISTIC PROBABILITY FOR  
A 1990 APPROVAL FOR QUINAPRIL. DATE WAS  
ACCEPTED.

01-OCT-90 FDA CONTACT MEMO  
CONTENT:

MEMO RE: CONFIRMATION OF RECEIPT  
CONTACT PERSON: SECRETARY TO RESNICK, C.  
TELEPHONE CONVERSATION RE: TO CONFIRM RECEIPT OF  
DRAFT SBA PLUS COMPUTER DISKETTE.

09-OCT-90 FDA CONTACT MEMO  
CONTENT:

MEMO RE: STATUS OF PHARMACOLOGY REVIEW  
CONTACT PERSON: RESNICK, CHARLES  
VISITED FDA RE: THE RECENTLY SUBMITTED SBA AND  
THE STATUS OF DR. VANARSDALE'S REVIEW OF THE  
QUINAPRIL NDA.

09-OCT-90 FDA CONTACT MEMO  
CONTENT:

MEMO RE: CONFIRM MEETING/STATUS CHECK  
CONTACT PERSON: BONGIOVANNI, KATHLEEN  
VISITED FDA RE: CONFIRMATION OF 12-OCT-90 FDA  
MEETING WITH DR. LIPICKY AND THE STATUS OF THE  
REVIEWS.

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17-OCT-90 FDA CONTACT MEMO  
CONTENT:

MEMO RE: REVIEW OF DRAFT SBA  
CONTACT PERSON: CHEN, SHAW, DR.  
VISITED FDA RE: REQUEST MINOR RE-WORDINGS OR  
ADDITIONAL DETAILS OR EXPLANATIONS AS FOLLOWS:  
1) A MORE DETAILED JUSTIFICATION FOR THE ONCE  
DAILY SLOW TITRATION STATEMENT.  
2) A LISTING OF DEATHS/WITHDRAWALS DURING THE  
CONTROLLED STUDY PERIODS VS. CONTROLS BROKEN  
OUT FOR HYPERTENSION AND CHF SEPARATELY.  
3) A LISTING OF SERIOUS AES DURING CONTROLLED  
PERIODS VS. PLACEBO AND ACTIVE CONTROLS.  
4) PROPOSED LABELING ACCOMPANY THE SBA.

24-OCT-90 FDA CONTACT MEMO  
CONTENT:

MEMO RE: QUESTIONS ON SBA  
CONTACT PERSON: FREEDMAN, BASIL, DR.  
TELEPHONE CONVERSATION RE: REQUEST STATUS OF  
REVIEW OF THE SBA. HE HAS FINISHED HIS REVIEW  
AND WAS WRITING HIS COMMENTS.

25-OCT-90 FDA CONTACT MEMO  
CONTENT:

MEMO RE: FOLLOW-UP TO 24/OCT/90 FDA CONTACT MEMO  
CONTACT PERSON: BONGIOVANNI, KATHLEEN  
TELEPHONE CONVERSATION RE: INFORMED HER OF  
CONVERSATION WITH DR. FREEDMAN REGARDING THE  
SBA.

25-OCT-90 16 LETTER RE: RESPONSE TO REQUEST FOR INFORMATION  
CONTENT:

LETTER TO: LIPICKY, RAYMOND J., M.D.  
RE: RESPONSE TO MS. KATHLEEN BONGIOVANNI SURVEY  
FORM REGARDING STUDIES IN PEDIATRIC PATIENTS.

30-OCT-90 FDA CONTACT MEMO  
CONTENT:

MEMO RE: FOLLOW-UP TO TELEPHONE CALL  
CONTACT PERSON: BONGIOVANNI, KATHLEEN, CSO  
TELEPHONE CONVERSATION RE: FOLLOW-UP TO 25-OCT-90  
TELEPHONE CALL.

31-OCT-90 17 LETTER RE: RESPONSE TO REQUEST FOR INFORMATION  
CONTENT:

LETTER TO: LIPICKY, RAYMOND J., M.D.  
VOLUME=10  
RE: RESPONSE TO 10-JUL-90 MEETING REQUEST  
REGARDING THE SUMMARY BASIS OF APPROVAL (SBA)  
SECTIONS 2, 3, 5, 6 AND 8 ARE AMENDED.

ITEM 1: AMENDMENT TO SECTION 2, COMPREHENSIVE  
SUMMARY

- ITEM 2: AMENDMENT TO SECTION 3, CHEMISTRY,  
MANUFACTURING AND CONTROLS.  
ITEM 3: AMENDMENT TO SECTION 5, NONCLINICAL  
PHARMACOLOGY AND TOXICOLOGY.

RR 740-02536

AUTHOR: RAPUNDALO, S. ET AL

DATE: 31-AUG-89

"COMPARATIVE EFFECTS OF QUINAPRIL AND QUINAPRILAT  
ON VARIOUS PROTEINASES"

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31-OCT-90 17 LETTER - CONTINUED  
CONTENT:

RR 740-02796

AUTHORS: RYAN, M.J.

OLSZEWSKI, B.J.

DATE: 26-FEB-90

"ANTI HYPERTENSIVE ACTIVITY OF QUINAPRIL GIVEN FOR  
14 DAYS TO CONSCIOUS SPONTANEOUSLY HYPERTENSIVE  
RATS"

RR 740-02694

AUTHOR: CASAD, B. ET AL

DATE: 1-SEP-89

"A MULTIPLE-DOSE STUDY TO ASSESS THE FUNCTIONAL  
INTERACTION OF QUINAPRIL (CI-906) AND  
HYDROCHLOROTHIAZIDE (CI-570) IN SALINE-LOADED  
SPONTANEOUSLY HYPERTENSIVE RATS"

31-OCT-90 17 LETTER - CONTINUED  
CONTENT:

RR 4192-00422

AUTHOR: NEUB, M. ET AL

DATE: 23-APR-90

"DOSE-PROPORTIONALITY AND SYSTEMIC EXPOSURE OF  
QUINAPRILAT IN MICE AND RATS FOLLOWING MULTIPLE  
ORAL DOSES OF QUINAPRIL (PRECLINICAL PROTOCOLS  
90-001 AND 90-002)"

ITEM 4: AMENDMENT TO SECTION 6, HUMAN  
PHARMACOKINETIC AND BIOAVAILABILITY.

RR 764-00523

AUTHOR: FERRY, J. ET AL

DATE: 16-MAY-86

"CLINICAL BIOPHARMACEUTICAL STUDY OF TWO NEW  
PROTOTYPE FORMULATION CAPSULES OF QUINAPRIL  
(CI-906) AND AN IMMEDIATE-RELEASE CAPSULE  
PROTOCOL 906-81"

31-OCT-90 17 LETTER - CONTINUED  
CONTENT:

ITEM 5: AMENDMENT TO SECTION 8, CLINICAL DATA.

RR 720-02593

AUTHOR: CANTER, D. ET AL

DATE: 25-APR-90

"AN EIGHT-WEEK, PLACEBO-CONTROLLED, DOUBLE-BLIND,  
MULTICENTER STUDY TO EVALUATE THE DOSE RESPONSE  
RELATIONSHIP OF QUINAPRIL (CI-906) WITH  
CONCOMITANT HYDROCHLOROTHIAZIDE IN PATIENTS  
WITH MILD TO MODERATE HYPERTENSION. (PROTOCOL  
906-241 THROUGH -19, -22 THROUGH -25, AND -27  
THROUGH -35)"

RR MEMO-420-00165

AUTHOR: RAULE, G.

DATE: 12-11-90

"QUINAPRIL IN HYPERTENSIVE PATIENTS WITH BRONCHIAL  
ASTHMA, DOUBLE-BLIND, ACUTE TEST VERSUS ENALAPRIL  
AND 12-WEEK FOLLOW-UP. (PROTOCOL 906-307,  
INTERIM REPORT)"

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DOC DATE	SER/SUPPL NO	TITLE
31-OCT-90	18	LETTER RE: SECOND DRAFT SUMMARY BASIS OF APPROVAL
CONTENT:		LETTER TO: LIPICKY, RICHARD J., M.D. RE: SECOND DRAFT OF THE SUMMARY BASIS OF APPROVAL PER 10-JUL-90 MEETING REQUEST.
01-NOV-90		FDA CONTACT MEMO
CONTENT:		MEMO RE: DESK COPY OF DRAFT SBA CONTACT PERSON: BONGIOVANNI, KATHLEEN, CSO VISITED FDA RE: 1) SBA. 2) NDA AMENDMENT - PRECLINICAL AND CLINICAL REPORTS THAT ARE OUTSTANDING. 3) LABELING. 4) MEDICAL REVIEWER'S COMMENTS. 5) BIOMETRICS.
02-NOV-90		LETTER RE: SBA
CONTENT:		LETTER TO: FRIEDMAN, BASIL, M.D. RE: SECOND DRAFT SUMMARY BASIS OF APPROVAL.
02-NOV-90	19	LETTER RE: DRAFT LABELING
CONTENT:		LETTER TO: LIPICKY, RAYMOND J., M.D. RE: A RUNNING TEXT OF THE DRAFT PACKAGE INSERT.
06-NOV-90		FDA CONTACT MEMO
CONTENT:		MEMO RE: FOLLOW-UP TO 1/NOV/90 VISIT CONTACT PERSON: BONGIOVANNI, KATHLEEN TELEPHONE CONVERSATION RE: FOLLOW-TO TO VISIT REGARDING THE FOLLOWING: 1) SBA - DR. FRIEDMAN HAS RECEIVED HIS COPY. 2) NDA AMENDMENT - BIOPHARMACEUTICAL SECTION AND LABELING. 3) LABELING - COULD SUBMIT F.P.L. IF WE WISHED. 4) MEDICAL REVIEWER'S COMMENTS - SUGGESTED WE MAKE A REQUEST FOR INFORMATION IMMEDIATELY. 5) BIOMETRICS - SHE PROMISED TO FOLLOW-UP ON THE STATUS OF THE REVIEW.
07-NOV-90	20	LETTER RE: RESPONSE TO REQUEST FOR INFORMATION
CONTENT:		LETTER TO: LIPICKY, RAYMOND J., M.D. RE: RESPONSE TO DR. BASIL FRIEDMAN'S COMMENTS REGARDING THE FOLLOWING: 1) QUINAPRIL IN PATIENTS WITH RENAL DYSFUNCTION. 2) ANALYSIS OF EFFICACY DATA WITH DBP > 95 VS. > 100 MM HG. 3) PROCEDURE FOR DOUBLE-BLIND CODE BREAKING. 4) QUINAPRIL DOSE RESPONSE. 5) QUALITY OF STUDY CONDUCT

- 6) EFFICACY - QUINAPRIL QD VS BID REGIMEN.
- 7) ADVERSE EVENTS - QUINAPRIL QD VS BID REGIMENS.
- 8) TIME-WINDOW FOR BID DOSING EVALUATION.
- 9) ADDITIONAL EFFICACY WITH DIURETIC THERAPY.
- 10) NONDIURETIC ANTIHYPERTENSIVE THERAPY IN  
LONG-TERM STUDIES.

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09-NOV-90 FDA CONTACT MEMO  
CONTENT:

MEMO RE: UPDATE ON STATUS OF RESEARCH REPORTS  
SENT TO FDA  
CONTACT PERSON: BONGIOVANNI, KATHLEEN  
TELEPHONE CONVERSATION RE: TO INFORM HER THAT THE  
FINAL TWO RESEARCH REPORTS WERE SHIPPED 12/NOV/90  
AND ASKED IF WE COULD SEND A COPY DIRECTLY TO  
DR. FRIEDMAN. SHE STATED "NO" AND SUGGESTED WE  
SEND A EXTRA COPY TO FDA, MARKED FOR DR. FIREDMAN  
REVIEW.

09-NOV-90 21 INFORMATION AMENDMENT  
CONTENT:

REVISED PAGES DRAFT SUMMARY BASIS OF APPROVAL  
PGS. 235 AND 238  
CROSS REFERENCE: REFERENCE #18

09-NOV-90 22 INFORMATION AMENDMENT  
CONTENT:

RR MEMO-710-02839  
AUTHOR: CANTER, D.A. ET AL  
DATE: 9-NOV-90  
"INITIAL SUMMARY OF RESULTS ON THE DOSE  
RESPONSE RELATIONSHIP, HUMORAL EFFECTS AND  
PHARMACOKINETICS OF QUINAPRIL IN SALT-REPLETE  
NORMOTENSIVE SUBJECTS (PROTOCOL 906-296)"

RR 720-02788  
AUTHOR: BEAMAN, B.A. ET AL  
DATE: 9-NOV-90  
"A 12-WEEK, DOUBLE-BLIND, PLACEBO-CONTROLLED,  
PARALLEL-GROUP, RANDOMIZED STUDY COMPARING  
THE ANTIHYPERTENSIVE EFFECTS OF ONCE DAYLY  
DOSES OF QUINAPRIL HYDROCHLORIDE (CI-906) WITH  
PLACEBO ON 24-HOUR BLOOD PRESSURE IN PATIENTS  
WITH MILD TO MODERATE HYPERTENSIVE (PROTOCOL  
906-327)"

11-NOV-90 FDA CONTACT MEMO  
CONTENT:

MEMO RE: STATUS OF REVIEW OF SBA  
CONTACT PERSON: CHEN, SHAW, DR.  
VISITED FDA RE: STILL REVIEWING THE FIRST VERSION  
OF THE SBA. HIS OVERALL IMPRESSION OF THE NDA  
IS THAT IT IS CLEARLY APPROVABLE FOR BID DOSING,  
BUT HAD NOT MADE HIS DECISION REGARDING ONCE-A-  
DAY YET.



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12-NOV-90 FDA CONTACT MEMO  
CONTENT:

MEMO RE: QUESTION ON 906-327 CLINICAL REPORT.  
CONTACT PERSON: FRIEDMAN, BASIL, DR.  
TELEPHONE CONVERSATION RE: QUESTION ON THE FINAL  
REPORT OF -327; TROUBLE FINDING SUPPORTIVE  
DOCUMENTATION IN THE APPENDICES FOR A FEW  
SUMMARY TABLES.

13-NOV-90 FDA CONTACT MEMO  
CONTENT:

MEMO RE: QUESTION ON RESEARCH REPORT FOR STUDY  
906-114  
CONTACT PERSON: CHEN, SHAW, DR.  
TELEPHONE CALL FROM FDA RE: REQUESTED  
CLARIFICATION ON THE FOLLOWING:  
1) THE NUMBER OF PATIENTS INCLUDED IN THE  
DIFFERENT ANALYSES SUMMARIZED ON TABLE 14.  
2) DIFFERENCE BETWEEN THE INTENT-TO-TREAT AND  
THE WEEKS 1 - 8 SAMPLES.  
3) COMMENT: HE HAD NOT YET REVIEWED THE  
REVISED DRAFT OF THE SBA.

15-NOV-90 FDA CONTACT MEMO  
CONTENT:

MEMO RE: REQUEST MEETING, REQUEST INFORMATION  
CONTACT PERSON: BONGIOVANNI, KATHLEEN  
TELEPHONE CONVERSATION RE: REQUEST THE  
FOLLOWING:  
1) MEETING TO DISCUSS THE STATUS OF THE NDA.  
MEETING WAS GRANTED FOR 16-NOV-90 AT 1 PM.  
2) MS BONGIOVANNI CALLED BACK WITH A QUESTION  
FROM DR. FRIEDMAN. HE REQUESTED THE  
SUBMISSION WHICH CONTAINED CLINICAL REPORTS  
OF -296 AND -327.  
SUBMISSION WAS SENT 9-NOV-90. SHE SHALL  
CHECK WITH THE DOCUMENT ROOM AND DR. FRIEDMAN.

15-NOV-90 LETTER FROM FDA RE: REQUEST INFORMATION  
CONTENT:

LETTER FROM: HUNG, H.M. JAMES, PH.D.  
PR. 906-12  
RE: REQUEST BLOOD PRESSURE DATA FOR THE FOLLOWING  
ANALYSES:  
1) INTENT-TO-TREAT  
2) INTENT-TO-TREAT, TIME WINDOW  
3) EVALUABLE PATIENTS, BASELINE TO LAST VISIT  
4) EVALUABLE PATIENTS, BASELINE TO LAST VISIT >=  
WEEK 4

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16-NOV-90 FDA CONTACT MEMO  
CONTENT:

MEMO RE: STATUS OF NDA  
CONTACT PERSON: BONGIOVANNI, KATHLEEN  
VISITED FDA RE: OFFERED A COPY OF THE LETTER FROM  
THE REVIEWING STATISTICIAN. DR. HUNG REQUESTED  
DATA FROM 906-12 ON IBM DISKS.

19-NOV-90 FDA CONTACT MEMO  
CONTENT:

MEMO RE: FURTHER COMMENTS ON DR. FRIEDMAN'S REVIEW  
OF QUINAPRIL SBA  
CONTACT PERSON: CHEN, SHAW  
TELEPHONE CONVERSATION RE: FURTHER REVIEW OF FDA'S  
COMMENTS ON THE SBA AS FOLLOWS:  
1) CHANGES COULD BE MADE AFTER APPROVAL.  
2) Q.D. IS BETTER THAN PLACEBO. IS IT UNIFORM  
ENOUGH?

20-NOV-90 FDA CONTACT MEMO  
CONTENT:

MEMO RE: TO PURSUE INSPECTION OF MOPS.  
CONTACT PERSON: KUMKUMIAN, CHARLES, DR.  
FDA MEETING RE: PER COMMISSIONER'S OFFICE, THE  
COMPLIANCE OFFICE HAS NOT RECIEVED THE REQUEST  
FOR INSPECTION FROM THE OFFICE OF DRUGS.  
DR. KUMKUMIAN PROMISED TO LOOK INTO THIS MATTER.

20-NOV-90 23 LETTER RE: RESPONSE TO REQUEST FOR INFORMATION  
CONTENT:  
LETTER TO: HUNG, H.M. JAMES, PH.D.  
RE: RESPONSE TO 15-NOV-90 WRITTEN REQUEST FOR  
AN IBM READABLE DATA DISKETTE FOR STUDY  
906-12.

21-NOV-90 FDA CONTACT MEMO  
CONTENT:

MEMO RE: FOLLOW-UP TO 20/NOV/90 VISIT  
CONTACT PERSON: KUMKUMIAN, CHARLES, DR.  
VISITED FDA RE: TO INQUIRE ABOUT THE REQUEST  
FOR INSPECTION IN OCTOBER AND THAT QUINAPRIL  
WAS NOW ON A PRIORITY LIST OF NEW DRUG DIVISIONS.  
FDA REQUEST CALL AFTER THE HOLIDAY TO CHECK  
ON THE REPORT FROM COMPLIANCE.

26-NOV-90 FDA CONTACT MEMO  
CONTENT:

MEMO RE: CONFIRM RECEIPT OF COMPUTER DISKETTES  
CONTACT PERSON: HUNG, JAMES, PHD  
TELEPHONE CONVERSATION RE: CONFIRM RECEIPT  
OF REQUESTED DATA ON STUDY 906-12.

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26-NOV-90 FDA CONTACT MEMO  
CONTENT:

MEMO RE: FOLLOW-UP TO 20/NOV/90 VISIT  
CONTACT PERSON: KUMKUMIAN, CHARLES, DR.  
TELEPHONE CONVERSATION RE: THE OFFICE OF  
COMPLIANCE HAS ASSURED HIM THAT QUINAPRIL  
WAS ON A SPECIAL PRIORITY INSPECTION LIST.

26-NOV-90 FDA CONTACT MEMO  
CONTENT:

MEMO RE: COMMENTS ON SECOND DRAFT OF SBA  
CONTACT PERSON: CHEN, SHAW, DR.  
TELEPHONE CALL FROM FDA RE: REQUEST CHANGES ON  
THE SECOND DRAFT OF THE SBA. ALSO REQUESTED  
THE FOLLOWING:  
1) ADVERSE EVENTS BROKEN DOWN BY DOSE.  
2) SBA REPLACEMENT PAGES ARE ACCEPTABLE.

27-NOV-90 FDA CONTACT MEMO  
CONTENT:

MEMO RE: UPDATE ON NDA ACTIVITIES  
CONTACT PERSON: BONGIOVANNI, KATHLEEN, CSO  
TELEPHONE CONVERSATION RE: INFORMED FDA THAT  
ALL REQUESTED CHANGES TO THE SBA WOULD ARRIVE  
THE NEXT DAY. ADVISED THAT THE 13-DEC-90  
ADVISORY COMMITTEE MEETING WOULD BE OF GREAT  
INTEREST TO US AND SUGGESTED OUR ATTENDANCE.

27-NOV-90 24 LETTER RE: REVISIONS TO SUMMARY BASIS OF APPROVAL  
CONTENT:

LETTER TO: LIPICKY, RAYMOND J., M.D.  
RE: RESPONSE TO 24-OCT-90 TELEPHONE CONVERSATION  
WITH DR. BASIL FREEDMAN REQUESTING REVISIONS  
TO THE SUMMARY BASIS OF APPROVAL. ADDITIONAL  
RESPONSE TO 26-NOV-90 QUESTIONS FROM DR. CHEN.

29-NOV-90 FDA CONTACT MEMO  
CONTENT:

MEMO RE: FINAL COMMENTS ON SBA  
CONTACT PERSON: CHEN, SHAW, DR.  
TELEPHONE CALL FROM FDA RE: HAD RECEIVED AND  
REVIEWED 27-NOV-90 SUBMISSION OF REPLACEMENT  
PAGES FOR THE SBA. ONE QUESTION ON THE  
REPLACEMENT PAGES AND FOUR ADDITIONAL COMMENTS  
ON THE SECOND DRAFT OF THE SBA.

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29-NOV-90 FDA CONTACT MEMO  
CONTENT:

MEMO RE: QUESTION CONCERNING CARCINOGENICITY DATA  
CONTACT PERSON: ALI, MIRZA, DR.  
TELEPHONE CALL FROM FDA RE: INQUIRED THE  
FOLLOWING:  
FDA: WHAT THE CAUSE OF DEATH CODE #4 "ANIMAL WAS  
SACRIFICED" MEANT?  
PARKE-DAVIS: CONFERRED WITH TOXICOLOGY, AND  
RETURNED CALL STATING CODE IN QUESTION MEANT  
THAT THE ANIMAL WAS SACRIFICED AT A  
SCHEDULED SACRIFICE.

03-DEC-90 FDA CONTACT MEMO  
CONTENT:

MEMO RE: STATUS OF CHEN/LIPICKY REVIEW  
CONTACT PERSON: BONGIOVANNI, KATHLEEN  
TELEPHONE CONVERSATION RE: REVIEWED THE FOLLOWING:  
1) ALL OF DR. CHEN'S COMMENTS HAD BEEN ADDRESSED.  
2) FDA INQUIRED WHEN OUR LAST SAFETY UPDATED WAS  
SUBMITTED. (SUBMITTED 25-JUL-90)  
3) FDA CALLED BACK TO CONFIRM SUBMISSION OF THE  
SAFETY UPDATE.  
4) FDA CALLED TO STATE THAT DR. CHEN WAS NOW  
REVIEWING OUR PACKAGE INSERT.

03-DEC-90 FDA CONTACT MEMO  
CONTENT:

MEMO RE: QUESTION ON REVIEW  
CONTACT PERSON: CHEN, SHAW, DR.  
TELEPHONE CALL FROM FDA RE: REQUESTED SPECIFIC  
LOCATIONS FOR PEAK B.P. MEASUREMENTS IN THE  
FOLLOWING PROTOCOLS:  
1) 906-11  
2) 906-30  
3) 906-114

04-DEC-90 FDA CONTACT MEMO  
CONTENT:

MEMO RE: NDA STATUS  
CONTACT PERSON: BONGIOVANNI, KATHLEEN  
TELEPHONE CONVERSATION RE: UNABLE TO FLY TO  
WASHINGTON LAST NIGHT, SENT OVERNIGHT TO DR. CHEN  
SUMMARY TABLES SELECTED FROM PREVIOUSLY SUBMITTED  
CLINICAL REPORTS.

05-DEC-90 FDA CONTACT MEMO  
CONTENT:

MEMO RE: REVIEW OF ACCUPRIL PATIENT INFORMATION  
BOOKLET  
CONTACT PERSON: FEATHER, KEN  
TELEPHONE CONVERSATION RE: REQUEST FEEDBACK ON A  
PATIENT INFORMATION BOOKLET WHICH CONTAINS NO  
LABELING AND LITTLE MENTION OF QUINAPRIL. SHALL  
DROP THE PIECE OFF AT HIS OFFICE ON FRIDAY

7-DEC-90.

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06-DEC-90 FDA CONTACT MEMO  
CONTENT:

MEMO RE: CONVEY DR. LIPICKY'S REQUEST FOR  
SAFETY UPDATE  
CONTACT PERSON: BONGIOVANNI, KATHLEEN, CSO  
TELEPHONE CALL RE: DR. KIPICKY DOES WANT A SAFETY  
UPDATE PRIOR TO APPROVAL. THE UPDATE IS NEEDED  
POST-APPROVALBE, BUT WOULD BE REQUIRED PRIOR TO  
FINAL APPROVAL.

06-DEC-90 25 LETTER RE: PROPOSED PACKAGE INSERT  
CONTENT:

LETTER TO: LIPICKY, RAYMOND J., M.D.  
CI-906  
RE: RESPONSE TO FDA REQUEST FOR INFORMATION  
REGARDING MORE DETAILED ANNOTATION TO OUR  
PROPOSED PACKAGE INSERT. SPECIFICALLY, THE  
ADVERSE EVENTS SECTION THAT INCLUDES REFERENCE  
TO THE NUMBER OF PATIENTS STUDIED IN TOTAL AS  
WELL AS VARIOUS SUBSETS. ALSO PROVIDE A GRAPHIC  
DISPLAY OF THE DIFFERENCE BETWEEN BLOOD  
PRESSURE MEASUREMENTS IN QUINAPRIL-TREATED  
PATIENTS VERSUS PLACEBO-TREATED PATIENTS IN THE  
24-HOUR BLOOD PRESSURE MONITORING STUDY (906-327)

06-DEC-90 26 LETTER RE: TELEPHONE CONVERSATION  
CONTENT:

LETTER TO: ALI, MIRZA DR.  
CI-906  
RE: TELEPHONE CONVERSATION OF 26-NOV-90;  
CLARIFICATION AS TO WHICH RATS IN THE  
CARCINOGENICITY STUDY DIED DUE TO GAVAGE ERRORS.  
NEW DATA DISKETTE ENCLOSED.

07-DEC-90 FDA CONTACT MEMO  
CONTENT:

MEMO RE: CONFIRM MS. BONGIOVANNI'S TELEPHONE CALL  
OF 06-DEC-90.  
CONTACT PERSON: LIPICKY, RAY DR.  
FDA MEETIN RE: IT WOULD NOT BE POSSIBLE FOR  
DR. TEMPLE TO APPROVE THE NDA THIS MONTH. HE  
PROJECTED "APPROVABLE" IN FEB/MAR AND "APPROVAL"  
IN MAR/APR. HE RECOMMENDED OUR COMPLETING THE  
SAFETY UPDATE NOW SO AS NOT TO EXTEND THE TIMING  
BETWEEN APPROVABLE AND APPROVAL. DISCUSSION  
OF THE MINIMUM ACCEPTABLE SAFETY UPDATE.

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07-DEC-90 FDA CONTACT MEMO  
CONTENT:

MEMO RE: DROP-OFF PATIENT INFORMATION BOOKLET FOR  
REVUEW  
CONTACT PERSON: PURVIS, WILLIAM  
FDA MEETING RE: MR. PURVIS AGREED TO PASS ON THE  
BOOKLET TO MR. FEATHER, BUT AT A SUPERFICIAL  
FIRST GLANCE, THE BOOKLET DID NOT APPEAR TO BE A  
PROBLEM.

07-DEC-90 FDA CONTACT MEMO  
CONTENT:

MEMO RE: OUTSTANDING ISSUES CONCERNING NDA REVIEW.  
CONTACT PERSON: CHEN, SHAW DR.  
RE: FDA MEETING WITH DR. MERINO, I. MARTIN, DR.  
CHEN AND MS. BONGIOVANNI TO DISCUSS CONCERNS  
WITH BIOMETRICS, PHARMACOLOGY, BIOPHARMACEUTICS,  
LABELING, SAFETY UPDATE, DIVISIONAL REVIEW,  
AND INSPECTION.

10-DEC-90 FDA CONTACT MEMO  
CONTENT:

MEMO RE: SBA QUESTION.  
CONTACT PERSON: CHEN, SHAW DR.  
TELEPHONE CONVERSATION RE: QUESTION ON NUMBERS OF  
PATIENTS IN TWO TABLES OF THE SBA. QUESTION  
CONCERNING THE PERCENTAGE OF PATIENTS WHO  
WITHDREW. BOTH QUESTIONS WERE RESOLVED.

10-DEC-90 FDA CONTACT MEMO  
CONTENT:

MEMO RE: STATUS OF BIOPHARM. & BIOMETRICS REVIEWS.  
CONTACT PERSON: BONGIOVANNE, KATHLEEN  
TELEPHONE CONVERSATION RE: NOTHING NEW ON THE  
STATUS OF THE BIOPHARM. OR BIOMETRICS REVIEWS  
SINCE MEETING ON FRIDAY.

10-DEC-90 27 LEETER RE: PROPOSED PACKAGE INSERT  
CONTENT:

LETTER TO: LIPICKY, RAYMOND, J., M.D.  
CI-906  
LETTER RE: REQUEST MADE ON 07-DEC-90 FOR UPDATED  
ANNOTATION FOR THE DOSAGE AND ADMINISTRATION  
SECTION OF THE PROPOSED PACKAGE INSERT. ENCLOSED  
IS PROPOSED TEXT AND THE APPROPRIATE REFERENCE.

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11-DEC-90  
CONTENT:

FDA CONTACT MEMO

MEMO RE: QUESTION ON 906-327 CLINICAL REPORT  
CONTACT PERSON: FRIEDMAN, BASIL, DR.  
TELEPHONE CALL FROM FDA RE: REQUEST ADDITIONAL  
INFORMATION REGARDING THE FINAL REPORT OF  
906-327. PARKE-DAVIS RETURNED CALL AND WERE  
ABLE TO ANSWER HIS QUESTIONS.

13-DEC-90  
CONTENT:

FDA CONTACT MEMO

MEMO RE: SAFETY UPDATE PROPOSAL  
CONTACT PERSON: BONGIOVANNI, DATHLEEN  
FDA MEETING RE: SAFETY UPDATE OUTLINE PROPOSAL  
FOR OUR FINAL SAFETY UPDATE; THIS IS TO BE  
DISCUSSED WITH DR. LIPICKY AND GET BACK TO US  
NEXT WEEK.

14-DEC-90  
CONTENT:

FDA CONTACT MEMO

MEMO RE: REVIEW OF ACCUPRIL PATIENT INFORMATION  
BOOKLET.  
FDA CONTACT PERSON: FEATHER, KEN  
FDA MEETING RE: CHANGES REQUESTED TO BOOKLET ON  
PAGES 7 & 8; AND THAT "ACCUPRIL IS A UNIQUE BLOOD  
PRESSURE MEDICATION" BE CHANGED TO "ADVERSE DRUG  
REACTIONS ARE USUALLY MILD AND TRANSIENT".

14-DEC-90  
CONTENT:

FDA CONTACT EMMO

MEMO RE: RECEIPT OF CI-955  
CONTACT PERSON: BONGIOVANNI, KATHLEEN  
TELEPHONE CONVERSATION RE: FDA INFORMED US CI-955  
NDA ARRIVED. DISCUSSED QUINAPRIL NDA REVIEW.  
ALSO CONFIRMED THAT DR. CHEN IS COMMITTED TO  
FINISHING HIS REVIEW AS SOON AS POSSIBLE.

19-DEC-90  
CONTENT:

FDA CONTACT MEMO

MEMO RE: ADVISORY COMMITTEE NOTIFICATION  
CONTACT PERSON: BONGIOVANNI, KATHLEEN, CSO  
TELEPHONE CONVERSATION RE: ALL SPONSORS OF  
APPROVED AND PENDING NDAS FOR ACE INHIBITORS  
INVITED TO CARDIO-RENAL ADVISORY COMMITTEE  
TO BE HELD 18-JAN-91.

QUESTIONED IF BENAZEPRIL HAD BEEN APPROVED.

INFORMED OUR PROPOSAL FOR THE QUINAPRIL SAFETY  
UPDATE WAS FINE.

THE NDA STILL HAS NOT LEFT THE DIVISION.



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20-DEC-90 FDA CONTACT MEMO  
CONTENT:

MEMO RE: FDA CONFERENCE DATE  
CONTACT PERSON: FORGARTY, PAULINE  
TELEPHONE CONVERSATION RE: OFFERED MEETING DATE  
OF 24-JAN-91 TO DISCUSS THE INDICATIONS THAT  
WERE FOUND APPROVABLE BY THE FDA. REQUESTED  
HOLD ON DATE BUT WOULD PREFER TO HAVE A MEETING  
IN EARLY FEBRUARY.

26-DEC-90 FDA CONTACT MEMO  
CONTENT:

MEMO RE: INVITE TO PRE-ADVISORY COMMITTEE MEETING  
CONTACT PERSON: MCDONALD, ZELDA  
TELEPHONE CALL FROM FDA RE: FDA'S INVITE TO  
PRE-ADVISORY COMMITTEE MEETING TO DISCUSS EFFECTS  
OF ANTIHYPERTENSIVE MEDICATIONS ON LEFT  
VENTRICULAR HYPERTROPHY (LVH) ON 18-JAN-91.

26-DEC-90 FDA CONTACT MEMO  
CONTENT:

MEMO RE: ANOTHER QUESTION ON SBA  
CONTACT PERSON: CHEN, SHAW, DR.  
TELEPHONE CALL FROM FDA RE: TO CLARIFY TWO POINTS  
IN THE SBA:  
1) PAGE 219, REQUEST SUPPORTIVE INFORMATION ON  
STATEMENT MADE IN THE FIRST TWO PARAGRAPHS.  
2) HE HAS MET WITH DR. LIPICKY. EXPECTS THE  
NDA TO BE AT DR. TEMPLE'S DESK EARLY NEXT  
WEEK.

27-DEC-90 FDA CONTACT MEMO  
CONTENT:

MEMO RE: QUINAPRIL HYDROCHLORIDE  
CONTACT PERSONS: WOLTERS, R., DR.  
CUNNINGHAM, D., MS.  
VISITED FDA RE: TO DISCUSS OUR LATEST EXPERIENCE  
WITH THE COMPLIANCE DIVISION (NEWARK DISTRICT).  
DISCUSSED THE FOLLOWING CHANGES TO BE SUBMITTED  
AS AN NDA AMENDMENT:  
1) REMOVAL OF THE 40MG TABLET FROM THE NDA.  
2) CHANGE THE COMMERCIAL BATCH SIZES OF THE 5,  
10 AND 20 MG TABLETS.  
3) REPLACE THE ILLUSTRATIVE MASTER BATCH RECORDS  
WITH THE COMMERCIAL MASTER BATCH RECORDS.  
4) REVISE BULK CONTAINER LABELS TO SPECIFY LOW  
HUMIDITY STORAGE.  
FDA ALSO REQUESTED THE FOLLOWING:  
1) COPY OF THE NOTICE OF ADVERSE FINDINGS LETTER.  
2) TABLES COMPARING THE BATCH FORMULA STRENGTH.  
3) COMPARISON OF MASTER BATCH RECORDS.  
4) COPIES OF THE COMMERCIAL MASTER BATCH RECORDS.  
5) ANALYTICAL DATA.

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27-DEC-90 FDA CONTACT PERSON  
CONTENT:

MEMO RE: PROVIDE ANSWER TO QUESTION OF 26-DEC-90.  
CONTACT PERSON: CHEN, SHAW  
FDA MEETING RE: PROVIDED ATTACHED DOCUMENTATION  
TO ANSWER QUESTIONS OF 26-DEC-90; AT REVIEW OF  
MATERIALS CHANGES WERE REQUESTED (SEE MEMO).  
DISCUSSION ALSO INCLUDED STATUS OF THE REST OF  
THE NDA REVIEW.

27-DEC-90 FDA CONTACT MEMO  
CONTENT:

MEMO RE: STATUS CHECK  
CONTACT PERSON: BONGIOVANNI, KATHLEEN  
FDA MEETING RE: UPDATED WITH CONVERSATION WITH  
DR. CHEN. DIVISIONAL RESPONSE TO BENAZEPRIL  
PROMOTIONAL PIECE WAS THAT IT WAS PROBABLY OK,  
EXCEPT QUESTIONED USE OF INDICATION FOR  
HYPERTENSION OF THE STOCKING ANNOUNCEMENT.

28-DEC-90 28 LETTER RE: DRAFT SUMMARY BASIS OF APPROVAL  
CONTENT:  
LETTER TO: LIPICKY, RAYMOND, J. M.D.  
CI-906  
RE: REQUESTED INFORMATION FOR DR. CHEN; ATTACHED  
ARE TWO REPLACEMENT PAGES WHICH HAVE INCORPORATED  
RESPONSES TO THESE QUESTIONS.

31-DEC-90 FDA CONTACT MEMO  
CONTENT:

MEMO RE: FINAL COMMENT ON NDA  
CONTACT PERSON: CHEN, SHAW  
TELEPHONE CONVERSATION RE: RECEIVED MATERIALS SENT  
TO HIM; INFORMATION WAS FINE WITH ONE QUESTION.  
QUESTION REGARDING 16 PATIENTS WITH NEUTROPHIL  
COUNT <1500 AND DID NOT RETURN TO NORMAL ON  
THERAPY IT IS POSSIBLE FOR THE NDA TO BE  
OUT OF THE DIVISION BY THE END OF THE WEEK.

31-DEC-90 29 LETTER RE: CHEMISTRY, MANUFACTURING AND CONTROLS  
CONTENT:

LETTER TO: LIPICKY, RAYMOND J., M.D.  
VOL. 6.1  
RE: TO AMEND THE CHEMISTRY, MANUFACTURING AND  
CONTROLS SECTION OF THE NDA AS FOLLOWS:  
1) COMMERCIAL BATCH FORMULAE FOR 5, 10 AND 20 MG  
ACCUPRIL TABLETS.  
2) COMPARISON OF NDA AND CURRENT MASTER BATCH  
RECORDS FOR THE 10 MG TABLET.  
3) CURRENT MASTER BATCH RECORDS FOR 5, 10 AND 20  
MG ACCUPRIL TABLETS.  
4) BULK CONTAINER LABELS.  
5) STABILITY DATA.  
6) NOTICE OF ADVERSE FINDINGS LETTER.

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02-JAN-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: CONFIRM RECEIPT OF TELEFAX  
CONTACT PERSON: CHEN, SHAW DR.  
TELEPHONE CONVERSATION RE: CONFIRMED RECEIPT OF  
TELEFAX WITH ANSWERS OF QUESTION ON 31-DEC-90.  
A REQUEST WAS ALSO MADE OF PATIENTS WITH  
ABNORMAL NEUTROPHIL COUNTS THAT NORMALIZED;  
INFORMATION WAS OBTAINED FROM DR. KNAPP.

03-JAN-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: STATUS CHECK  
CONTACT PERSON: BONGIOVANNI, KATHLEEN  
TELEPHONE CONVERSATION RE: RECOMMENDATION THAT ANY  
OUTSTANDING DOCUMENTATION BE SUBMITTED AS SOON AS  
POSSIBLE SO THAT THE APPROVABLE LETTER WILL HAVE  
ALL APPROPRIATE REFERENCES. THIS WAS AGREED.

03-JAN-91 30 LETTER RE: GENERAL CORRESPONDENCE  
CONTENT:

LETTER TO: LIPICKY, RAYMOND, J. M.D.  
CI-906  
RE: REQUEST FOR ADDITIONAL INFORMATION FOR 16  
PATIENTS EXPERIENCING NEUTROPENIA AT THE LAST  
STUDY VISIT; TABLE WITH INFORMATION IS ENCLOSED.  
WE ALSO CONFIRM THAT PATIENT #8 WAS NOT COUNTED  
IN ABOVE INFORMATION.  
ALSO PROVIDED INFORMATION OF 44 PATIENTS WHOSE  
LOW NEUTROPHIL COUNTS RETURNED TO NORMAL HAD  
COUNTS < 100 DURING THE STUDY.

04-JAN-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: REQUEST FOR NARRATIVE SUMMARIES  
CONTACT PERSON: CHEN, SHAW DR.  
TELEPHONE CONVERSATION RE: NARRATIVES SUMMARIES  
FOR NINE PATIENTS WITH WBC < 2000/MM3; FIFTEEN  
PATIENTS WITH NEUTROPHIL COUNTS < 1000/MM3; AND  
NINE PATIENTS WHOSE NEUTROPHIL COUNT WAS <  
1000/MM3, THEN SUBSEQUENTLY RETURNED TO NORMAL;  
ARE TO BE SENT AS SOON AS POSSIBLE.

08-JAN-91 31 LETTER RE: CHEMISTRY, MANUFACTURING AND CONTROLS  
CONTENT:

LETTER TO: LIPICKY, RAYMOND J. M.D.  
CI-906  
RE: OUR PENDING NDA (19-885) FOR ACCUPRIL TABLETS,  
SUBMITTED ON 26-JAN-89 AND THE AMENDMENT TO THE  
CHEMISTRY, MANUFACTURING AND CONTROLS SECTION OF  
THE NDA DATED 31-DEC-90.

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08-JAN-91 32 LETTER RE: GENERAL CORRESPONDENCE  
CONTENT:

LETTER TO: LIPICKY, RAYMOND J. M.D.  
CI-906  
RE RESPONSE TO: FDA CONTACT MEMO DATED 04-JAN-91  
FROM DR. CHEN; REQUESTED INFORMATION ENCLOSED.

09-JAN-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: DELIVER DESK COPIES OF NDA AMENDMENT  
CONTACT PERSON: WOLTERS, ROBERT  
FDA MEETING RE: DELIVERED DESK COPIES OF 2  
AMENDMENTS (08-JAN-91 AND 31-DEC-90) TO THE  
QUINAPRIL NDA CMC SECTION.  
INFORMED DR. WOLTERS INSPECTION OF THE MOPS  
MANUFACTURING FACILITY BEGAN 08-JAN-91.

09-JAN-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: RESPONSE TO BENAZAPRIL PRE-APPROVAL AD  
CONTACT PERSON: CAVANAUGH, TOM  
TELEPHONE CONVERSATION RE: THE BENAZAPRIL  
ANNOUNCEMENT (FAX'ED TO FDA) WAS VIOLATIVE FOR A  
PRE-APPROVAL AD. FDA WOULD BE CONTACTING CIBA-  
GEIGY DIRECTLY TO DISCUSS THIS PROMOTIONAL  
ACTIVITY.

09-JAN-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: NDA STATUS  
CONTACT PERSON: BONGIOVANNI, KATHLEEN  
FDA MEETING RE: DELIVERED DESK COPY OF THE  
NARRATIVES REQUESTED BY DR. CHEN THAT WERE  
SUBMITTED TO THE NDA.  
FDA INFORMED THAT  
1) BIOMETRICS REVIEW IS FINALIZED AND SIGNED  
2) DR. LIPICKY WOULD NOT WAIT FOR BIOPHARM.  
REVIEW WHICH IS STILL OUTSTANDING.  
3) DR. LIPICKY IS STILL DOING SECONDARY REVIEW  
OF PHARMACOLOGY.  
INFORMED FDA THE CMC NDA AMENDMENTS; THEIR  
RATIONALE AND OF THE ONGOING MOPS SITE INSPECTION

09-JAN-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: CONFIRM 18-JAN-91 ATTENDANCE  
CONTACT PERSON: MCDONALD, ZELDA  
FDA MEETING RE: CONFIRMED THAT P-D WOULD BE  
ATTENDING THE 18-JAN-91 PM MEETING ON LV  
HYPERTROPHY AND ANTIHYPERTENSIVES. 5 WILL BE IN  
ATTENDANCE.

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10-JAN-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: FOLLOW-UP TO 09-JAN-91 VISIT  
CONTACT PERSON: BONGIOVANNI, KATHLEEN  
TELEPHONE CONVERSATION RE: CONVERSATION WITH  
MR. CAVANAUGH WHO INFORMED US HE FELT THE  
BENAZAPRIL AD WAS VIOLATIVE.  
REQUESTED MEETING WITH DR. LIPICKY, MARTIN AND  
MERINO NEXT WEEK.

14-JAN-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: CONFIRM MEETING  
CONTACT PERSON: BONGIOVANNI, KATHLEEN  
TELEPHONE CONVERSATION RE: CONFIRMED MEETING WITH  
DRS. LIPICKY, CHEN, MARTIN, AND MERINO ON 18-JAN  
AT 8:45 AM.

18-JAN-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: INFORM RESULTS OF SITE INSPECTION.  
CONTACT PERSON: WOLTERS, ROBERT  
FDA MEETING RE: INSPECTION OF MOPS FOR QUINAPRIL  
WENT WELL AND A 483 WAS NOT ISSUED.

18-JAN-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: QUINAPRIL NDA ISSUES.  
CONTACT PERSON: BONGIOVANNI, KATHLEEN  
FDA MEETING RE: MOPS INSPECTION WENT WELL AND A  
483 WAS NOT ISSUED.  
REQUESTED NEW CLASS LABELING FOR ACE INHIBITORS  
FOR USE IN PREGNANCY; SHE WILL SEND COPY WHEN  
FINALIZED.  
NEW MEDICAL REVIEWER ASSIGNED TO QUINAPRIL;  
DR. SOMANI.

18-JAN-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: STATUS OF NDA REVIEW.  
CONTACT PERSON: LIPICKY, RAY DR.  
FDA MEETING RE: DISCUSSION OF STATUS OF NDA REVIEW  
IN THE CARDIO-RENAL DIVISION.  
MEETING HELD WITH DRS. MERINO, MARTIN, LIPICKY,  
CHEN AND MS. BONGIOVANNI; SEE MEMO FOR DISCUSSION

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22-JAN-91  
CONTENT:

FDA CONTACT MEMO

MEMO RE: FOLLOW-UP ON DR. SOMANI'S REQUEST.  
CONTACT PERSON: BONGIOVANNI, KATHLEEN  
TELEPHONE CONVERSATION RE: DISCUSSION OF HOW WE  
WILL BE ANSWERING DR. SOMANI'S REQUEST FOR  
INFORMATION.  
FAX TO BE SENT TO US ON 24-JAN ABOUT SPONSORS FOR  
THE ACE ADVISORY COMMITTEE; WE ARE TO RESPOND BY  
25-JAN.  
SHE IS TO CHECK WITH DR. FENICHEL ABOUT CHANGES  
IN ACE PREGNANCY BOILERPLATE. IF NONE WILL FAX  
CURRENT LABELING.  
DISCUSSED OPTIONS OF SPEEDING UP DR. VANARSDALE'S  
PHARMACOLOGY REVIEW.

24-JAN-91  
CONTENT:

FDA CONTACT MEMO

MEMO RE: AVAILABILITY OF INFORMATION ON ADVISORY  
COMMITTEE.  
CONTACT PERSON: BONGIOVANNI, KATHLEEN  
TELEPHONE CONVERSATION RE: FDA FAX'ED TO US;  
-LATEST APPROVED PREGNANCY WORDING FOR VASOTEC  
(FURTHER CHANGES MAY OCCUR)  
-PROPOSED LIST OF QUESTIONS FOR CARDIO-RENAL  
ADVISORY COMMITTEE MEETING ON ACE INHIBITORS  
DOCUMENTS ARE ATTACHED

25-JAN-91  
CONTENT:

FDA CONTACT MEMO

MEMO RE: CONFIRM ADVISORY COMMITTEE PARTICIPATION  
CONTACT PERSON: BONGIOVANNI, KATHLEEN, CSO  
TELEPHONE CONVERSATION RE: TO INFORM FDA THAT  
PARKE-DAVIS WILL PARTICIPATE IN THE ACE  
ADVISORY COMMITTEE AND ARE WILLING TO PRESENT  
UNMASKED DATA ON QUINAPRIL.

29-JAN-91  
CONTENT:

FDA CONTACT MEMO

MEMO RE: CONFIRM ATTENDANCE AT FEBRUARY 20 PRE-  
ADVISORY COMMITTEE MEETING  
CONTACT PERSON: BONGIOVANNI, KATHLEEN, CSO  
TELEPHONE CONVERSATION RE: CONFIRMING PARKE-DAVIS  
ATTENDANCE TO 20-FEB-91 PRE-ADVISORY COMMITTEE  
MEETING AND ACTUAL MEETING TO BE HELD ON  
JUNE 6-7, 1991.

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01-FEB-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: INFORM OF GLP INSPECTION  
CONTACT PERSON: BONGIOVANNI, KATHLEEN  
TELEPHONE CONVERSATION RE: INFORMED HER OF ONGOING  
GLP INSPECTION OF THE QUINAPRIL RAT CARCINOGEN-  
ICITY STUDY; SHE WAS NOT AWARE OF THIS.  
ALSO INFORMED HER THAT DR. MERINO HAS BEEN IN  
TOUCH WITH MARY DOUG TYSON AND DR. WEISSINGER  
CONCERNING DR. VANARSDALE.

04-FEB-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: INFORM RESULTS OF PRE-CLINICAL INSPECTION  
CONTACT PERSON: BONGIOVANNI, KATHLEEN  
TELEPHONE CONVERSATION RE: INSPECTION OF THE RAT  
CARCINOGENICITY STUDY WAS COMPLETE AND NO -483  
WILL BE ISSUED. DR. VANARSDALE REQUESTED THIS  
INSPECTION IN SEP-90. INSPECTORS FOUND NOTHING  
OF SIGNIFICANCE AND WILL CALL DR. VANARSDALE  
WITH THEIR FINDINGS.

05-FEB-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: INFORM OF CLINICAL SITE INSPECTION AND  
ASK FOR RAMAPRIL LABELING.  
CONTACT PERSON: BONGIOVANNI, KATHLEEN  
TELEPHONE CONVERSATION RE: DR. MITCHELL OF  
ALBUQUERQUE, NM, 906-238-5 HAS RECEIVED  
NOTIFICATION BY THE FDA HOUSTON OFFICE OF  
INSPECTION OF HIS SITE THIS WEEK.  
CONFIRMED THE APPROVAL OF RAMAPRIL, APPROVAL  
LETTER AND APPROVED LABELING WILL BE SENT.

05-FEB-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: TO DISCUSS THE STATUS OF THE PHARMACOLOGY  
REVIEW FOR THE QUINAPRIL NDA.  
CONTACT PERSON: WEISSINGER, JUDI  
MEETING RE: FOLLOW-UP ON STATUS OF PHARMACOLOGY  
REVIEW FOR QUINAPRIL NDA. SHE WILL FOLLOW-UP WITH  
THE CARDIORENAL DIVISION TODAY. REVIEWED THE  
HISTORY AS WELL AS RECENT GLP INSPECTION  
REGARDING QUINAPRIL.

05-FEB-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: QUINAPRIL PHARMACOLOGY REVIEW  
CONTACT PERSON: WEISSINGER, JUDI  
TELEPHONE CONVERSATION RE: SHE HAD VISITED  
CARDIORENAL DIVISION AND FOUND THE QUINAPRIL  
PHARMACOLOGY/TOXICOLOGY REVIEW HAS BEEN TOP  
PRIORITY SINCE OCT-89. SHE AGREED THAT THE REVIEW  
TIME WAS TOO LONG AND WILL FOLLOW-UP WITH DR.  
VAN ARSDALE DIRECTLY. CONFIRMED THAT THE BIOASSAY

WAS CLEAN, WILL FOLLOW-UP TO DETERMINE IF THEIR  
ARE ANY SCIENTIFIC ISSUES. SHE WILL DO HER BEST  
TO GET REVIEW COMPLETED.



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06-FEB-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: FOLLOW-UP TO INFORMATION ON CLINICAL  
INVESTIGATIONS.  
CONTACT PERSON: BONGIOVANNI, KATHLEEN  
TELEPHONE CONVERSATION RE: SIX CLINICAL  
INVESTIGATORS WERE CHOSEN FOR INSPECTION (SEE  
MEMO).  
ALSO DISCUSSED STRATEGIES FOR SUBMISSION OF THE  
FINAL SAFETY UPDATE.

06-FEB-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: RAMIPRIL  
CONTACT PERSON: BONGIOVANNI, KATHLEEN  
MAIL SENT RE: RAMIPRIL APPROVAL LETTER AND PACKAGE  
INSERT FOR USE IN PREPARING ACCUPRIL LABELING.

06-FEB-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: QUESTIONS ON NDA AMENDMENTS.  
CONTACT PERSON: SAMARA, EMIL DR.  
TELEPHONE CONVERSATION RE: REVIEW OF NDA  
COMPLETED; CURRENTLY REVIEWING OUR RECENT  
AMENDMENTS, HE HAD 4 MINOR QUESTIONS.  
QUESTION 1 WAS ANSWERED IMMEDIATELY, QUESTIONS  
2-4 WERE ANSWERED IN A RETURN CALL ON 07-FEB.  
SEE MEMO FOR QUESTIONS AND ANSWERS.  
STILL HAS CONCERNS WITH THE VALIDATION OF THE  
ANALYTICAL METHODOLOGY. SPECIFIC CONCERNS  
REVOLVED AROUND THE THREE METHODS HE REVIEWED.  
SEE MEMO FOR THOSE CONCERNS.  
RECOMMENDED WE WAIT UNTIL WE RECEIVE DEFICIENCY  
LETTER AND THEN REPLY.

06-FEB-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: QUESTIONS ON NDA AMENDMENTS  
CONTACT PERSON: SAMARA, EMIL, DR.  
TELEPHONE CALL FROM FDA RE: REQUEST THE FOLLOWING  
INFORMATION:  
1) DEFINITION OF OUR USE OF THE TERM "MARKET-  
IMAGE".  
2) FORMULATIONS USED IN STUDIES 906-342, -305,  
-328 WHICH WERE SUBMITTED TO THE NDA ON  
7/25/90.  
3) REASON FOR SUBMISSION OF REPORT ON STUDY  
906-81 IN SUBMISSION OF 10/31/90.  
4) SITE FOR ANALYTICAL METHODS IN ABOVE STUDIES.

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11-FEB-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: NDA STATUS  
CONTACT PERSON: BONGIOVANNI, KATHLEEN  
MEETING RE: DR. VANARSDER, PHARMACOLOGY REVIEW  
REMAINS OUTSTANDING.  
LOOKING FOR 20-FEB SUBMISSION TO ANSWER DR.  
SAMARA QUESTIONS. THIS IS ALSO THE DATE PLANNED  
TO SUBMIT THE FINAL SAFETY UPDATE AND REVISED  
DRAFT LABELING TO NDA.  
CONFIRMED MEETING TO DISCUSS THE ACE ADV. CMTE.  
WILL BE 20-FEB AT 10:00 AM IN ROOM 16A29.

12-FEB-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: QUESTION ON CARCINOGENICITY DATA  
CONTACT PERSON: VANARSDER, WILLIAM DR.  
TELEPHONE CONVERSATION RE: DR. RESNICK IS  
REVIEWING STATISTICIAN'S REVIEW OF QUINAPRIL RAT  
AND MOUSE CARCINOGENICITY STUDIES. THE HISTORICAL  
DATA ON TUMOR INCIDENCES IN OUR CONTROL GROUPS OF  
RATS AND MICE CAN NOT BE LOCATED. WILL FIND OUT  
AND GET BACK TO HIM.  
ASKED HIS STATUS ON THE REST OF THE REVIEW; HE IS  
WORKING ON IT.

14-FEB-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: FOLLOW-UP TO DR. VANARSDER'S REQUEST FOR  
"HISTORICAL CONTROLS" FOR RAT  
CARCINOGENICITY STUDY.  
CONTACT PERSON: RESNICK, CHARLES PH.D.  
TELEPHONE CONVERSATION RE: TO CLARIFY REQUEST FOR  
HISTORICAL CONTROL INFORMATION FROM DR. VANARSDER  
BASED ON RECENTLY COMPLETED STATISTICAL REVIEW OF  
THE CARCINOGENICITY STUDIES ISSUES NEED TO BE  
ADDRESSED. STATISTICAL ANALYSIS NOTED A TREND  
WITH DOSE IN FEMALE RATS (SEE MEMO FOR LISTED  
TUMORS). BECAUSE OF THE FINDING IN THE REVIEW A  
REQUEST WAS MADE TO PROVIDE HISTORICAL CONTROL  
INFORMATION (SEE MEMO FOR INFORMATION). DR.  
RESNICK WOULD LIKE TO PUT THIS ISSUE TO REST AS  
SOON AS POSSIBLE. THIS COULD BE CRITICAL PATH TO  
APPROVAL, NEED FOR QUICK TURNAROUND.

19-FEB-91 33 SAFETY UPDATE  
CONTENT:  
VOLUMES = 14

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19-FEB-91 34 LETTER RE: ANALYTICAL METHODOLOGIES  
CONTENT:

LETTER TO: LIPICKY, RAYMOND J. M.D.  
CI-906

RE RESPONSE TO QUESTIONS FROM DR. SAMARA PER  
TELEPHONE CONVERSATION ON 07-FEB:

INFORMATION ON ANALYTICAL METHODOLOGIES

1) 4192-00292, HPLC, FRIEBURG

VALIDATION ON STABILITY IN SHIPPING AND  
RECOVERY METHOD. LIST OF CLINICAL STUDIES  
WHICH UTILIZED THIS METHOD.

2) 764-00441, GC FOR HYMAN PLASMA  
SITE WHERE VALIDATION WAS PERFORMED. BLANK  
CHROMATOGRAM. VALIDATION ON RECOVERY/STABILITY  
LIST OF CLINICAL STUDIES WHICH UTILIZED THIS  
METHOD.

3) 764-01083, GC FOR HUMAN URINE  
VALIDATION ON RECOVERY/STABILITY. BLANK  
CHROMATOGRAM. LIST OF CLINICAL STUDIES WHICH  
UTILIZED THIS METHOD.

REQUESTED INFORMATION ATTACHED, EXCEPT FOR BLANK  
CHROMATOGRAPHS, PROVIDED IN 1-2 WEEKS.

20-FEB-91  
CONTENT:

FDA CONTACT MEMO

MEMO RE: FOLLOW-UP TO REQUEST FOR HISTORICAL  
CONTROLS FROM RAT CARCINOGENICITY STUDY.

CONTACT PERSON: RESNICK, CHARLES PH.D

MEETING RE: TO CLARIFY HIS REQUEST FOR "MEAN  
SURVIVAL TIME" IN HISTORICAL VS. CONCURRENT  
CONTROLS.

WE QUESTIONED STATUS OF DR. VAN ARSDEL'S REVIEW.  
END OF FEBRUARY COULD BE POSSIBLE FOR COMPLETION  
OF REVIEW.

20-FEB-91  
CONTENT:

FDA CONTACT MEMO

MEMO RE: DELIVERY OF DESK COPIES

CONTACT PERSON: BONGIOVANNI, K.

MEETING RE: MET AND DISCUSSED FOLLOWING:

1 DELIVERED 2 DESK COPIES OF THIRD SAFETY UPDATE.

2 DELIVERED 2 DESK COPIES OF RESPONSE TO ASSAY  
VALIDATION QUESTIONS FROM BIOPHARMACEUTICS.

3 BRIEFLY OUTLINED REQUEST FOR HISTORICAL  
CONTROLS FROM PHARMACOLOGY/TOXICOLOGY REVIEWER.

4 INDICATED THAT WE WOULD PROVIDE THE REQUESTED  
OVERVIEW OF THE CHF SUBMISSION AND IND LOCATION  
OF CHF PROTOCOLS EARLY NEXT WEEK.

WE DID NOT INTEND TO PURSUE ANY ADDITIONAL  
INDICATION AT THIS TIME.

5 REGARDING QUIET STUDY; WE WOULD OPEN SEPARATE  
IND FOR PATIENT POPULATION, AND REQUEST REVIEW  
OF PROPOSED PROTOCOL.

6 NO SPECIFIC UPDATE OF THE STATUS OF DR.  
VAN ARSDEL'S TOXICOLOGY REVIEW.

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20-FEB-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: PRE-ADVISORY COMMITTEE PLANNING MEETING -  
ACE INHIBITORS  
CONTACT PERSON: LIPICKY, RAYMOND DR.  
MEETING RE: MEETING OPENED WITH SUMMARY OF MOST  
RECENT TELEFAX (ATTACHED) HIGHLIGHTING FDA'S  
CHANGING AGENDA CONCERNING ACE INHIBITORS.  
ATTENDEES ASKED FOR MORE SPECIFICS ON REQUESTED  
DATA AND QUESTIONS TO BE ADDRESSED.  
SEE MEMO FOR LIST OF ISSUES DISCUSSED.

25-FEB-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: TABLET EXPIRATION DATING  
CONTACT PERSON: CUNNINGHAM, D. MS.  
TELEPHONE CONVERSATION RE: SHE HAD COMPLETED HER  
REVIEW AO AMENDMENT AND HAD NO QUESTIONS. SHE  
ALSO STATED OUR REQUEST FOR 36-MONTH  
EXPIRATION ON TABLET WAS APPROVED.  
BRENNAN IS TO CONTACT COMPLIANCE DISTRICT OFFICE  
TO CONFIRM RECOMMENDATION FOR APPROVAL WAS  
FORWARDED TO WASHINGTON COMPLIANCE OFFICE AS SHE  
HAS NOT RECIEVED INSPECTION REPORT.

25-FEB-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: FOLLOW-UP TO QUESTIONS ON NDA AMENDMENTS  
CONTACT PERSON: SAMARA, EMIL DR.  
TELEPHONE CONVERSATION RE: STILL NEEDS ADDITIONAL  
INFORMATION ON RECOVERY, NOT NECESSARILY  
ABSOLUTE RECOVERY.  
WE SHOULD WAIT RO RECEIVE LETTER FROM DIVISION  
BEFORE RESPONDING FURTHER, ISSUES WOULD NOT HOLD  
UP APPROVAL.

25-FEB-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: COMMENT ON SBA  
CONTACT PERSON: CHEN, SHAW DR.  
MEETING RE: HE MIGHT ASK US TO AGAIN UPDATE THE  
QUINAPRIL SBA, HE COULD FAX US THE PAGES HE  
WANTED CHANGED AS THIS WOULD NOT BE A PROBLEM.

25-FEB-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: MISCELLANEOUS TOPICS  
CONTACT PERSON: BONGIOVANNI, KATHLEEN  
MEETING RE: PROMISED TO CALL WHEN SHE RECEIVED  
DR. SAMARA'S RESPONSE TO OUR RECENT SUBMISSION.  
OUR RESPONSE TO DR. RESNICK'S REQUEST WOULD BE  
TO THEM ON 26-FEB.  
DISCUSSION OF NEXT PRE-MEETING FOR CARDIO-RENAL  
ADVISORY COMMITTEE.

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25-FEB-91 35 LETTER RE: STATISTICAL ANALYSIS: PHARMACOLOGY  
CONTENT:

LETTER TO: LIPICKY, RAYMOND J. M.D.  
CI-906  
RE RESPONSE TO 14-FEB-91 REQUEST:  
ATTACHMENT TO THIS LETTER, WE HAVE PROVIDED THE  
HISTORICAL CONTROL INFORMATION IN FEMALE RATS  
AS REQUESTED.

28-FEB-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: NEXT MEETING OF PRE-ADVISORY COMMITTEE  
PLANNING GROUP.  
CONTACT PERSON: BONGIOVANNI, KATHLEEN  
FAX RE: MATERIALS PROMISED TO BE SENT TO US LAST  
WEEK WILL BE SENT BY FAX TOMORROW.  
NEXT PLANNING MEETING SCHEDULED FOR 20-MAR-91,  
AT 1:00 PM IN 13B39.

28-FEB-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: STATUS OF QUINAPRIL REVIEW  
CONTACT PERSON: RESNICK, CHARLES DR.  
TELEPHONE CONVERSATION RE: CONFIRMED RECEIPT OF  
RECENT SUBMISSION IN RESPONSE TO HIS QUESTION ON  
HISTORICAL CONTROLS IN CARCINOGENICITY STUDIES.  
ALSO ALERTED US TO ANOTHER POSSIBLE CONCERN,  
REGARDING HIGHER DOSE LEVELS USED IN THESE  
STUDIES (SEE MEMO).  
CONFIRMED THAT DR. VANARSDEL WILL NOT BE THROUGH  
WITH HIS REVIEW IN FEBRUARY. AGREED MARTIN CAN  
STOP TO CHECK NEXT WEEK ON HIS ESTIMATE OF THE  
COMPLETION OF THE DRAFT PHARMACOLOGY REVIEW.  
PASSED ON FOR HIS INFORMATION ONLY THAT DRS.  
MERINO AND CRESSWELL WILL BE WITH DRS. PECK AND  
TEMPLE ON 01-MAR AND LIKELY THEIR CONCERN WOULD  
BE RAISED OVER PHARMACOLOGY REVIEW.

28-FEB-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: REQUESTS FROM THIRD SAFETY UPDATE.  
CONTACT PERSON: CHEN, SHAW DR.  
TELEPHONE CONVERSATION RE: REQUEST FOR FOLLOWING  
TABLE TO HELP HIS REVIEW OF 20-FEB SUBMISSION  
OF THIRD SAFETY UPDATE.  
FROM PLACEBO CONTROLLED STUDIES, PROVIDE RATE  
(PERCENT)  
- WITHDRAWALS DUE TO AES  
- NON-FATAL, SERIOUS EVENTS  
- DEATHS  
- TOTAL ADVERSE EVENTS  
SEE MEMO FOR COMPLETE REQUEST FOR INFORMATION.  
HE MIGHT HAVE SUGGESTED CHANGES TO THE SBA READY  
NEXT WEEK.  
WISHED TO KNOW WHY 7 DEATHS ARE LISTED FOR  
QUINAPRIL FROM CONTROLLED STUDIES IN THE SAFETY

UPDATE, SBA LISTS 9 QUINAPRIL DEATHS.

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01-MAR-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: FOLLOW-UP TO 28-FEB REQUEST.  
CONTACT PERSON: CHEN, SHAW DR.  
TELEPHONE CONVERSATION RE: REQUEST DATA FOR  
PATIENTS WITHDRAWING, DYING, SUFFERING A SERIOUS  
AE OR SUFFERING ANY AE. HE WOULD NOW LIKE THESE  
PERCENTAGES FOR ALL QUINAPRIL PATIENTS. THESE  
DATA MAY AGAIN BE BROKEN DOWN BY HYPERTENSION  
AND CHF.

01-MAR-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: DELAY IN PHARMACOLOGY REVIEW.  
CONTACT PERSON: TEMPLE, DR.  
MEETING RE: DISCUSSION OF DR. VAN ARSDALE DELAY IN  
THE PHARMACOLOGY REVIEW. MENTIONED WE WOULD  
APPRECIATE HIS RAPID REVIEW OF THE NDA WHEN  
RECEIVED. HE WILL LOOK INTO THE MATTER.

04-MAR-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: CONFIRM ATTENDANCE AT 20-MAR ACE  
INHIBITOR MEETING/QUIET PROTOCOL  
SUBMISSION.  
CONTACT PERSON: BONGIOVANNI, K. MS.  
TELEPHONE CONVERSATION RE: TO CONFIRM OUR  
ATTENDANCE AT NEXT PLANNING MEETING TO BE HELD  
20-MAR-91 AT 1:00 PM IN 13B39 AT THE PARKLAWN  
BUILDING.  
INDICATED SUBMITTING THE DRAFT QUIET STUDY  
PROTOCOL FOR REVIEW, WOULD LIKE TO MEET WITH  
DR. LIPICKY TO DISCUSS STUDY. SHE WILL CHECK ON  
POSSIBLE DATES. BOTH AGREED WE COULD SEND NEW  
PROTOCOL TO EXISTING IND WITH UNDERSTANDING THAT  
WE WOULD OPEN SEPARATE IND WHEN PROTOCOL WAS  
FINALIZED.

04-MAR-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: AGENDA FOR NEXT MEETING ON ACE INHIBITORS  
CONTACT PERSON: LIPICKY, RAYMOND  
TELEPHONE (FAX) RE: SEE ATTACHED COMMUNICATION  
REGARDING UPCOMING ACE INHIBITOR MEETING,  
INCLUDING DATE OF THE NEXT WORK GROUP MEETING  
(20-MAR, 1:00 PM, 13B39).

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CONTENT:

FDA CONTACT MEMO

MEMO RE: FOLLOW-UP TO EARLIER DISCUSSION  
CONTACT PERSON: RESNICK, CHARLES  
MEETING RE: FDA SUGGESTED WE SUBMIT THE ATTACHED  
INTERNAL MEMO REGARDING COMPARATIVE ANIMAL-HUMAN  
SERUM LEVELS, TO THE NDA. SUGGESTED HOW OUR  
RESPONSE SHOULD NOTE, (SEE MEMO).  
TO CHECK BACK WITH HIM ON WEDNESDAY TO DISCOVER  
THE OUTCOME OF MEETING WITH DR. VAN ARSDEL.

04-MAR-91  
CONTENT:

FDA CONTACT MEMO

MEMO RE: STATUS OF NDA  
CONTACT PERSON: BONJIOVANNI, KATHLEEN  
MEETING RE: HAS HEARD NOTHING OF DR. VAN ARSDEL'S  
REVIEW.  
PROVIDED HER DESK COPY OF 3/4 AMENDMENT TO THE 3RD  
SAFETY UPDATE REQUESTED BY CHEN.  
BRIEFLY DISCUSSED HER FAX ON 01-MAR OF THE ACE  
ADVISORY COMMITTEE MEETING.

04-MAR-91  
CONTENT:

36 LETTER RE: SAFETY UPDATE

LETTER TO: LIPICKY, RAYMOND M.D.  
CI-906  
RE: RESPONSE TO REQUEST FROM DR. CHEN ON 28-FEB  
AND 01-MAR. ENCLOSED ARE ATTACHMENTS OF REQUESTED  
INFORMATION.

05-MAR-91  
CONTENT:

FDA CONTACT MEMO

MEMO RE: CLARIFICATION OF DATA IN FINAL SAFETY  
UPDATE.  
CONTACT PERSON: FRIEDMAN, BASIL DR.  
TELEPHONE CONVERSATION RE: FRIEDMAN CALLED TO ASK.  
1) ON P.171 OF THE UPDATE DOES THE COLUMN HEADED  
"QUINAPRIL" INCLUDE DIURETIC TREATED PATIENTS?  
2) ON P.174, WHAT DOES PROT A1 AND PROT B MEAN?  
CONFERING WITH LLOYD KNAPP, RETURNED CALL TO ANSWER  
HIS QUESTIONS.

05-MAR-91  
CONTENT:

37 LETTER RE: PLASMA CONCENTRATIONS

LETTER TO: LIPICKY, RAYMOND M.D.  
CI-906  
RE: AVAILABILITY OF INFORMATION ON THE PLASMA  
CONCENTRATIONS OBTAINED IN THE RAT AND MOUSE  
CARCINOGENICITY STUDIES.



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06-MAR-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: FOLLOW-UP TO RESPONSE TO SAFETY UPDATE  
CONTACT PERSON: CHEN, SHAW M.D.  
MEETING RE: CONFIRMED HIS RECEIPT OF DISK COPY OF  
OUR 04-MAR SUBMISSION; OFFERED TO PICK UP ANY  
CHANGES TO THE SBA HE WOULD LIKE MADE.  
HE WOULD LIKE AN EXPLANATION OF APPARENT  
INCONSISTENCY OF THE THIRD SAFETY UPDATE AND THE  
SBA REGARDING TOTAL DEATHS.  
WE SHOULD BE PREPARED TO DEFEND; DURING LABELING;  
THAT OUR FOOD INTERACTION STUDY WAS CONDUCTED  
WITH A NON-FDA STANDARD MEAL.

07-MAR-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: STATUS OF NDA  
CONTACT PERSON: RESNICK, CHARLES  
MEETING RE: DR. VANARSDEL'S COMPLETION OF THE  
DRAFT OF PHARMACOLOGY REVIEW BY 15-MAR.

08-MAR-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: ADDITIONAL SAFETY UPDATE QUESTIONS.  
CONTACT PERSON: CHEN, SHAW DR.  
MEETING RE: HE HAS REVIEWED HIS SECONDARY REVIEW  
WITH DR. LIPICKY. THREE AREAS SHOULD BE  
ADDRESSED PRIOR TO THE NDA'S TRIP TO DR. TEMPLE:  
GOUT, RENAL FUNCTION, AND DR. FRIEDMAN'S REVIEW,  
SEE MEMO FOR COMPLETE DISCUSSION.

11-MAR-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: QUESTIONS ON 3RD SAFETY UPDATE.  
CONTACT PERSON: CHEN, SHAW  
TELEPHONE CONVERSATION RE: ANOTHER ERROR IN THE  
QUINAPRIL THIRD SAFETY UPDATE, SEE MEMO

12-MAR-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: REQUEST FOR ADDITIONAL SAFETY TABLE  
CONTACT PERSON: CHEN, SHAW DR.  
TELEPHONE CONVERSATION RE: REQUEST THAT WE  
PROVIDE ADDITIONAL INFORMATION IN REGARDS TO  
ADVERSE EVENTS. SEE MEMO

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13-MAR-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: QUESTION ON SAFETY UPDATE/SBA  
CONTACT PERSON: CHEN, SHAW DR.  
TELEPHONE CONVERSATION RE: QUESTION ON THE SAFETY  
UPDATE LABORATORY VALUE SHIFT TABLE; WHICH WAS  
ANSWERED.  
REQUESTED UPDATE TO SBA APPENDIX B.4 SUBMITTED TO  
THE NDA ON 08-JAN-91. SHOULD BE UPDATED THROUGH  
THE THIRD SAFETY UPDATE.

13-MAR-91 38 LETTER RE: GENERAL CORRESPONDENCE  
CONTENT:

LETTER TO: LIPICKY, RAYMOND M.D.  
CI-906  
RE: REPONDING TO QUESTIONS RECEIVED ON 06-MAR,  
08-MAR AND 12-MAR-91 CONCERNING OUR PENDING NDA

14-MAR-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: FOLLOW-UP ON STATUS OF PHARMACOLOGY  
REVIEW.  
CONTACT PERSON: RESNICK, CHARLES  
MEETING RE: 15/MAR STILL REALISTIC FOR DR.  
VANARSDDEL'S COMPLETION OF THE DRAFT PHARMACOLOGY  
REVIEW. HIS REVIEW OF THE STUDIES IS COMPLETE,  
CURRENTLY COMPLETING WRITTEN REVIEW.  
QUINAPRIL LISTED OUT OF THE DIVISION IN MARCH.

15-MAR-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: STATUS OF PHARMACOLOGY REVIEW  
CONTACT PERSON: BONGIOVANNI, K. MS.  
MEETING RE: CHECK ON STATUS OF DR. VAN ARSKEL'S  
PHARMACOLOGY REVIEW, SHE HAD NOT RECEIVED, WILL  
CHECK ON STATUS AND CALL.

18-MAR-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: FOLLOW-UP TO PHARMACOLOGY  
CONTACT PERSON: BONGIOVANNI, DATHLEEN  
TELEPHONE CONVERSATION RE: AT 1 PM MS. BONGIOVANNI  
STILL HAD NOT RECIEVED THE PHARMACOLOGY REVIEW;  
BUT PROMISED TO CALL WHEN IT ARRIVED.

18-MAR-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: QUESTION ON 13-MAR RESPONSE TO HIS  
EARLIER QUESTIONS.  
CONTACT PERSON: CHEN, SHAW DR.  
TELEPHONE CONVERSATION RE: WOULD LIKE DISCREPANCY  
IN THE THIRD SAFETY UPDATE (APPENDIX 8.7)  
CLARIFIED.

LABORATORY ABNORMALITIES INCLUDED BOTH HYPOKALEMIA  
AND DECREASED POTASSIUM; IS THIS CORRECT?  
DRS. KNAPP AND MARTIN CLARIFIED DISCREPANCIES.  
SCHEDULED MEETING ON WEDNESDAY 20-MAR AT 9:30 AM  
TO DISCUSS UPDATE TO SBA APPENDIX B.4 AND MERGING  
OF RELATED AE TERMINOLOGY.

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19-MAR-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: QUESTION FROM BIOPHARMACEUTICS REVIEW.  
CONTACT PERSON: CHEN, SHAW DR.  
TELEPHONE CONVERSATION RE: LIKE TO KNOW IF ANY  
DATA WERE AVAILABLE ON EFFICACY IN HEPATICLY  
IMPAIRED PATIENTS.  
DURING MEETING ON 20-MAR HE WAS PROVIDED WITH THE  
ATTACHED PAGES FROM A RESEARCH REPORT IN THE NDA.  
INFORMED THAT B/P DATA ARE NOT AVAILABLE.

19-MAR-91 39 LETTER RE: GENERAL CORRESPONDENCE  
CONTENT:

LETTER TO: LIPICKY, RAYMOND M.D.  
CI-906  
RE: RESPONDING TO QUESTIONS RECIEVED ON 11-MAR,  
18-MAR NAD 19-MAR; AND THE SAFTEY UPDATE  
SUBMITTED 19-FEB-91. QUESTIONS WERE FROM  
DR. SHAW CHEN.

20-MAR-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: REVIEW RESPONSES TO VARIOUS RECENT  
REQUESTS.  
CONTACT PERSON: CHEN, SHAW DR.  
MEETING RE: UPDATE DRS. KNAPP AND CHEN ON OUR  
RESPONSE TO RECENT QUESTIONS, ALL SATISFIED.  
REVIEWED REQUEST TO COLLAPSE VARIOUS AE TERMS TO  
PROVIDE A TRUER PICTURE OF THE AE PROFILE OF  
QUINAPRIL. AGREED PRIORITY SHOULD BE THE AE  
LISTING FROM CONTROLLED CLINICAL TRIALS,  
ESPECIALLY IF IMPACTS LABELING.  
DR. CHEN HAD NOT RECEIVED DRAFT PHARMACOLOGY  
REVIEW FROM DR. VANARSDDEL.  
DR. CHEN RECEIVED BIOPHARMACEUTICS FINAL REVIEW.  
PROVIDED US WITH COMMENTS AND LABELING SECTIONS  
OF THE REVIEW (ATTACHED).

20-MAR-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: STATUS OF VANARSDDEL REVIEW.  
CONTACT PERSON: RESNICK, CHARLES  
MEETING RE: STILL WAITING FOR DR. VANARSDDEL  
PHARMACOLOGY REVIEW.

20-MAR-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: NDA STATUS  
CONTACT PERSON: BONGIOVANNI, KATHLEEN  
MEETING RE: NO NEW INFORMATION ON THE PHARMACOLOGY  
REVIEW. CONFIRMED THAT BENAZAPRIL WAS NOT YET  
APPROVED.

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21-MAR-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: FOLLOW-UP TO 20-MAR MEETING ON ACE  
ADVISORY COMMITTEE.  
CONTACT PERSON: BONGIOVANNI, KATHLEEN  
TELEPHONE CONVERSATION RE: CONFIRM OUR PSEUDONYM  
FOR QUINAPRIL TO BE USED DURING THE ADVISORY  
COMMITTEE PRESENTATION. AGREED ON "BESTAPRIL".  
ALSO REQUESTED A CONTACT FOR PMA CONCERNING THE  
COST OF CONSULTANTS.  
NEXT MEETING OF GROUP WILL BE 19-APR AT 9 AM.

22-MAR-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: FOLLOW-UP TO QUESTION ON WBC/NEUTROPHIL  
COUNTS - THIRD SAFETY UPDATE.  
CONTACT PERSON: CHEN, SHAW M.D.  
TELEPHONE CONVERSATION RE: REQUEST THAT A  
DENOMINATOR BE PROVIDED SO THAT HE COULD  
CALCULATE THE INCIDENCE OF LOW WBC AND NEUTROPHIL  
COUNTS. WE WILL PROVIDE THE EXACT NUMBER EARLY  
NEXT WEEK. WE PROVIDED AN ESTIMATE UNTIL THAT  
TIME.  
NOTED THE DISCREPANCY IN SBA AND THE THIRD SAFETY  
UPDATE RESULTED FROM INCLUDING CONTROLLED AND  
UNCONTROLLED STUDIES IN THE FORMER, AND ONLY  
CONTROLLED STUDIES IN THE LATTER.

22-MAR-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: QUESTION ON 19-MAR SUBMISSION IN RESPONSE  
TO EARLIER QUESTION.  
CONTACT PERSON: CHEN, SHAW DR.  
TELEPHONE CONVERSATION RE: LABORATORY MEASUREMENTS  
IN THE THIRD SAFETY UPDATE VARIED. WHY IS LATER  
NUMBER LOWER?  
REQUESTED DENOMINATOR TO USE TO CALCULATE THE NEW  
INCIDENCE FIGURES FOR NEUTROPENIA AND DECREASED  
WBC.

25-MAR-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: QUINAPRIL NDA  
CONTACT PERSON: TEMPLE, ROBERT DR.  
TELEPHONE CONVERSATION RE: DR. VAN ARSDALE HAD  
COMPLETED THE PHARMACOLOGY REVIEW AND WAS  
DISCUSSING IT WITH HIS SUPERVISOR, DR. RESNICK.  
DR. LIPICKY WOULD HAVE IT SHORTLY.

DR. TEMPLE'S REVIEW SHOULD NOT BE LONG AND SHOULD  
NOT BE ANY PROBLEM.

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26-MAR-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: CHECK STATUS OF PHARMACOLOGY REVIEW.  
CONTACT PERSON: BONGIOVANNI, K.  
TELEPHONE CONVERSATION RE: CHECK OF STATUS OF  
PHARMACOLOGY REVIEW; NO NEWS TO PROVIDE, BUT WILL  
CALL AS SOON AS SHE RECEIVED THE REVIEW.  
MEETING WITH DR. LIPICKY REGARDING THE QUIET  
PROTOCOL, DATE OF 12-APR AT 9:30 AM HAS BEEN  
PROPOSED. WILL CONFIRM THIS DATE WITH P-D  
REPRESENTATIVES.  
DISCUSSION OF DR. CHERYL GRAHAM'S LEAVING.

28-MAR-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: MINUTES FROM LAST ACE INHIBITOR PLANNING  
MEETING.  
CONTACT PERSON: BONGIOVANNI, K.  
FAXED INFORMATION RE: ATTACHED ARE FDA MINUTES OF  
LAST PLANNING MEETING (20-MAR) IN PREPARATION FOR  
A CARDIO-RENAL ADVISORY COMMITTEE MEETING TO BE  
HELD 06-JUN AND 07-JUN.

28-MAR-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: UPDATE STATUS OF PHARMACOLOGY REVIEW.  
CONTACT PERSON: RESNICK, CHARLES PH.D.  
TELEPHONE CONVERSATION RE: UPDATE ON DR. VAN  
ARSDEL'S PROGRESS COMPLETING THE PHARMACOLOGY  
REVIEW. STATUS HAS NOT CHANGED; HE WOULD NOT  
SPECULATE ON A COMPLETION DATE.

28-MAR-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: CONFIRM ATTENDANCE AT REVIEW OF QUIET  
PROTOCOL.  
CONTACT PERSON: BONGIOVANNI, K.  
TELEPHONE CONVERSATION RE: CONFIRMED OUR  
ATTENDANCE AT A MEETING TO DISCUSS THE QUIET  
PROTOCOL ON 12-APR AT 9:30 AM IN ROOM 16B45.  
SEE MEMO FOR LIST OF ATTENDING FDA MEMBERS.  
STILL NO WORD ON THE STATUS OF THE PHARMACOLOGY  
APPROVAL.

01-APR-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: CLARIFY STATUS OF PHARMACOLOGY REVIEW.  
CONTACT PERSON: RESNICK, CHARLES  
TELEPHONE CONVERSATION RE: INFORMED HIM THAT  
DR. TEMPLE INFORMED DR. MERINO ON 25-MAR THAT  
DR. VANARSDDEL HAD COMPLETED HIS REVIEW;  
DR. SPIVEY STATED THAT LAST WEEK HIS REVIEW WAS  
STILL NOT COMPLETED.  
DR. RESNICK PROMISED TO LOOK INTO IT AND GET BACK

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01-APR-91 40 RE: GENERAL CORRESPONDENCE  
CONTENT:

LETTER TO: LIPICKY, RAYMOND M.D.  
CI-906  
RE: RESPONDING TO 08-MAR AND 22-MAR QUESTIONS.  
THESE QUESTIONS CONCERNED INFORMATION PROVIDED  
IN THE THIRD SAFETY UPDATE.

02-APR-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: DELIVER DESK COPIES OF REFERENCE NO. 40,  
RESPONSE TO DR. CHEN'S QUESTIONS.  
CONTACT PERSON: BONGIOVANNI, K. VIA IN PERSON  
SUMMARY: I DELIVERED DESK COPIES OF OUR RESPONSE  
TO DR. CHEN'S QUESTIONS CONCERNING COSTART CODING  
AND DENOMINATOR FOR WBC/NEUTROPHIL ANALYSES. DR.  
CHEN WAS OUT OF HIS OFFICE UNTIL APR-08.  
MS. BONGIOVANNI ASKED ABOUT THE AVAILABILITY OF  
HARD COPY OF DATA ON QUINAPRIL FOR THE ACE  
ADVISORY COMMITTEE MEETING. I INDICATED THAT EARLY  
NEXT WEEK WAS OUR TARGET. SHE SAID THAT APR-12 WAS  
THE LAST DATE WHICH WOULD ALLOW THE AGENCY ENOUGH  
TIME TO REVIEW PRIOR TO THE NEXT PLANNING MEETING  
(APR-19).

04-APR-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: STATUS OF PHARMACOLOGY REVIEW.  
CONTACT PERSON: BONGIOVANNI, K. VIA TELEPHONE  
SUMMARY: KATHLEEN BONGIOVANNI CALLED ON APR-04, ON  
BEHALF OF DR. TEMPLE AND SAID THAT THE DRAFT  
PHARMACOLOGY REVIEW HAS BEEN COMPLETED BY DR.  
VAN ARSDALE AND IS NOW AVAILABLE FOR REVIEW BY  
DRS. CHEN AND LIPICKY.

04-APR-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: FOLLOW-UP ON QUINAPRIL REVIEW  
CONTACT PERSON: BONGIOVANNI, K. VIA IN PERSON  
SUMMARY: MS. BONGIOVANNI CONFIRMED THAT THE PHARM-  
ACOLOGY REVIEW WAS NOW WITH DR. LIPICKY. SHE FELT  
DR. CHEN AND DR. LIPICKY WILL WORK ON THE  
SECONDARY REVIEW TOGETHER. WHILE IT WILL CLEARLY  
BE DR. CHEN'S TOP PRIORITY UPON HIS RETURN FROM  
VACATION ON APR-08, SHE COULD NOT GUARANTEE DR.  
LIPICKY WILL WORK ON IT IMMEDIATELY. THERE IS  
ACTUALLY ONLY A FEW DAYS OF WORK LEFT; IT IS HOPED  
THAT THE NDA WILL BE WITH DE. TEMPLE THIS MONTH.

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04-APR-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: FOLLOW-UP TO APR-01 CONTACT.  
CONTACT PERSON: RESNICK, CHARLES VIA IN PERSON  
SUMMARY: DR. RESNICK INFORMED ME THAT DR. VAN ARSDEL COMPLETED HIS DRAFT REVIEW. IT WAS NOW WITH DR. LIPICKY; DR. RESNICK DID NOT REVIEW IT. I EXPLAINED THAT I THOUGHT DR. CHEN WOULD DO THE SECONDARY (DIVISIONAL) REVIEW. DR. RESNICK FELT DR. LIPICKY WISHED TO SEE THE REVIEW DUE TO ITS DELAY.  
I THANKED DR. RESNICK FOR THE INFORMATION. HE WILL LIKELY NOT BE INVOLVED AGAIN UNTIL THE FINAL LABELING DISCUSSIONS OR FINALIZATION OF THE SBA.

09-APR-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: FINAL (?) QUESTION ON NDA REVIEW.  
CONTACT PERSON: CHEN, SHAW DR. VIA TELEPHONE  
SUMMARY: DR. CHEN WANTED TO KNOW IF WE HAD EVER RESPONDED TO HIS EARLIER REQUEST CONCERNING THE PROPER "N" FOR NEUTROPHILS AND WBC. HE WAS INFORMED THAT THE SUBMISSION WAS DELIVERED ON APRIL 2. DR. CHEN CHECKED HIS COPY AND APOLOGIZED FOR THE OVERSIGHT.  
DR. CHEN ALSO WISHED TO ASK OUR DEFINITION OF "END-OF-STUDY". IF A LABORATORY VALUE RETURNED TO NORMAL AT THE END-OF-STUDY, WAS THE PATIENT STILL ON DRUG? AFTER CHECKING WITH DR. KNAPP, DR. CHEN WAS INFORMED THAT, EXCEPT IN RARE INSTANCES, PATIENTS WERE ON DRUG DURING THIS FINAL LABORATORY MEASUREMENT.  
DR. CHEN HAS SEEN, BUT NOT YET REVIEWED CAREFULLY, THE DRAFT PHARMACOLOGY REVIEW. HE WILL NEED TO MEET WITH DR. LIPICKY TO INCORPORATE THE PHARMACOLOGY SECTION INTO HIS SECONDARY (DIVISIONAL) REVIEW. CONTINUED: SEE CENTRAL FILE COPY.

09-APR-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: LIST OF ATTENDEES AT QUIET PROTOCOL REVIEW.  
CONTACT PERSON: BONGIOVANNI, K. VIA TELEPHONE  
SUMMARY: I CALLED MS. BONGIOVANNI TO TELL HER THAT WE WOULD HAVE SIX REPRESENTATIVES AT THE MEETING ON APRIL 12. WE WILL HAVE REPRESENTATIVES FROM CLINICAL DEVELOPMENT, BIOMETRICS, AND REGULATORY AFFAIRS. A LIST OF ATTENDEES WILL BE SUBMITTED TO FDA TOMORROW.  
ON A SEPARATE MATTER, I INDICATED THAT WE WOULD LIKELY HAVE DATA FOR THE ACE-1 ADVISORY COMMITTEE MEETING TO THE AGENCY ON APRIL 12, IF NOT THEN, ON MONDAY APRIL 15.



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11-APR-91 LETTER RE: CARDIOVASCULAR RENAL DRUG ADVISORY COMMITTEE  
CONTENT:

LETTER TO: BONGIOVANNI, KATHLEEN MS.  
RE: ATTACHED ARE THE DATA WHICH WE AGREED TO  
PROVIDE FOR THE UPCOMING CARDIOVASCULAR AND RENAL  
DRUG ADVISORY COMMITTEE MEETING IN JUNE. WE  
BELIEVE WE HAVE PRESENTED THE DATA IN THE FORMAT  
AGREED UPON AT OUR PLANNING MEETING ON MARCH 20,  
1991.  
DR. LLOYD KNAPP (CLINICAL DEVELOPMENT), AND I WILL  
BE IN ATTENDANCE AT THE NEXT MEETING TO BE HELD ON  
APRIL 19, 1991. IF YOU HAVE QUESTIONS CONCERNING  
THE PROVIDED INFORMATION, PLEASE DON'T HESITATE TO  
CONTACT ME

11-APR-91 41 LETTER RE: GENERAL CORRESPONDENCE  
CONTENT:

LETTER TO: LIPICKY, RAYMOND M.D.  
RE: WE ARE RESPONDING TO QUESTIONS AND COMMENTS  
FROM THE BIOPHARMACEUTICS DIVISION REGARDING OUR  
PENDING NDA 19-885 FOR ACCUPRIL (QUINAPRIL  
HYDROCHLORIDE) TABLETS. WE RECEIVED THESE COMMENTS  
VIA DR. SHAW CHEN, OF YOUR DIVISION, ON MARCH 20,  
1991.  
FOR EASE OF REVIEW, WE HAVE REPEATED THE QUESTIONS  
AND COMMENTS FOLLOWED BY OUR RESPONSES IN AN  
ATTACHMENT TO THIS LETTER. WE BELIEVE WE HAVE  
UNDERSTOOD AND ADEQUATELY ADDRESSED THESE  
QUESTIONS AND COMMENTS FROM THE BIOPHARMACEUTICS  
DIVISION.  
IF WE CAN BE OF FURTHER ASSISTANCE, PLEASE DO NOT  
HESITATE TO CONTACT THE UNDERSIGNED AT 313/996-  
7756.  
CONTINUED: SEE CENTRAL FILE COPY FOR ATTACHMENTS.

12-APR-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: PROVIDE COPIES OF DATA FOR ACE INHIBITOR  
ADVISORY COMMITTEE MEETING  
CONTACT PERSON: BONGIOVANNI, K. VIA IN PERSON  
SUMMARY: I DELIVERED A COPY OF DATA FOR QUINAPRIL  
("BESTAPRIL") WHICH WILL BE PRESENTED BY FDA AT  
THE JUNE 6-7 ADVISORY COMMITTEE MEETING. THE  
FORMAT, ECT., WILL BE REVIEWED AT THE NEXT  
PLANNING MEETING AT FDA ON APRIL 19, 1991 (DRS.  
KNAPP & SPIVEY TO ATTEND).  
I THEN ASKED MS. BONGIOVANNI IF DR. DERN (MEDICAL  
REVIEWER) HAD ANY FEEDBACK ON THE CLINICAL SECTION  
OF THE ACCURETIC NDA, AS WE HAD ALREADY RECEIVED  
QUESTIONS ON THE CMC SECTION. SHE SAID SHE WOULD  
CHECK AND LET ME KNOW.

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12-APR-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: STATUS OF QUINAPRIL REVIEW.  
CONTACT PERSON: BONGIOVANNI, K. VIA IN PERSON  
SUMMARY: MS. BONGIOVANNI INDICATED THAT DR. CHEN  
AND DR. LIPICKY HAD NOT YET MET TO REVIEW THE  
PHARMACOLOGY SECTION OF THE DIVISIONAL REVIEW. ONE  
REASON FOR THE DELAY WAS DR. LIPICKY'S COMMAND  
PERFORMANCE WITH DR. TEMPLE BEFORE A CONGRESSIONAL  
PANEL (SEE ATTACHED SUMMARY). MS. BONGIOVANNI WAS  
CONFIDENT, HOWEVER, THAT THE NDA WOULD BE TO  
DR. TEMPLE BY THE END OF APRIL.

12-APR-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: STATUS OF QUINAPRIL INSPECTION  
CONTACT PERSON: WOLTERS, ROBERT VIA IN PERSON  
SUMMARY: WHILE I WAS STANDING IN THE HALLWAY AT  
THE FDA, DR. WOLTERS ASKED ME IF WE HAD EVER  
RECEIVED OUR SITE INSPECTION OF MOPS FOR  
QUINAPRIL. I INFORMED HIM THAT WE HAD IN JANUARY  
AND PASSED WITH FLYING COLORS. DR. WOLTERS STILL  
HAD NOT RECEIVED NOTIFICATION FROM COMPLIANCE.  
I NOTED THAT WE ARE NOW ONLY A FEW WEEKS AWAY FROM  
APPROVAL AND THAT I WAS CONCERNED HE HAD NOT YET  
HEARD FROM COMPLIANCE. I PROMISED TO FOLLOW UP ON  
OUR END WITH NEWARK AND/OR COMPLIANCE HEAD-  
QUARTERS. DR. WOLTERS THANKED ME FOR THE EFFORT.

12-APR-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: REQUEST FOR SAMPLE SLIDE FOR ADVISORY  
COMMITTEE PLANNING MEETING (4-19-91).  
CONTACT PERSON: FENICHEL, R. M.D. VIA IN PERSON  
SUMMARY: DR. FENICHEL STOPPED ME IN THE HALLWAY  
AT FDA TO DISCUSS FORMATS FOR SLIDE PREPARATION  
FOR OUR NEXT ADVISORY COMMITTEE PLANNING MEETING  
(4-19-91). WE DISCUSSED THE VARIOUS FORMATS  
(INCLUDING HARVARD GRAPHICS, WHICH WE USE) AND HE  
REQUESTED AN EXAMPLE SLIDE FOR THE NEXT MEETING.  
HE WILL PROVIDE A SLIDE ALONG WITH THE NECESSARY  
DESCRIPTION OF COLORS, ECT.

15-APR-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: QUESTION ON BIOPHARM. RESPONSE SUBMITTED  
4/12.

CONTACT PERSON: CHEN, SHAW DR. VIA TELEPHONE  
SUMMARY: DR. CHEN AND DR. SAMARA (FROM BIOPHARM.)  
HAD BOTH REVIEWED OUR APRIL 11 SUBMISSION WHICH  
CONTAINED OUR RESPONSES TO DR. SAMARA'S REVIEW OF  
THE NDA. DR. SAMARA NEEDED CLARIFICATION OF THE  
LOCATION OF THE PK PARAMETERS REFERENCED IN  
RESPONSE NUMBER 3. ALL OTHER RESPONSES WERE  
REVIEWED WITHOUT FURTHER COMMENT. DR. CHEN  
SUGGESTED WE TELEPHONE DR. SAMARA DIRECTLY WITH

THIS INFORMATION (443-0260).  
DR. CHEN STILL HAD NOT MET WITH DR. LIPICKY  
CONCERNING THE PHARMACOLOGY REVIEW, THOUGH HE HAS  
REVIEWED IT HIMSELF. HE IS NOW AWARE OF WHERE THE  
ISSUES MIGHT BE. HE ALSO AGREED WE ARE GETTING  
QUITE CLOSE TO SENDING THE NDA TO DR. TEMPLE.

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15-APR-91 FDA CONTACT MEMO  
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MEMO RE: STATUS OF QUINAPRIL INSPECTION  
CONTACT PERSON: CUNNINGHAM, D. VIA TELEPHONE  
SUMMARY: I CALLED MS. CUNNINGHAM TO INFORM HER  
THAT MR. D. MULLIGAN (COMPLIANCE DIVISION, NEWARK  
DISTRICT), THE INSPECTOR FOR QUINAPRIL, CONFIRMED  
THAT THE INSPECTION REPORT WAS SENT TO METRO PARK  
NORTH (COMPLIANCE DIVISION) IN FEBRUARY OF THIS  
YEAR. SHE SAID THAT SHE COULD NOT CONTACT  
COMPLIANCE DIRECTLY BUT HAD TO GO THROUGH LINDA  
CARTER (CDER I). SHE SUGGESTED THAT I CONTACT  
COMPLIANCE DIRECTLY. I TOLD HER THAT PREVIOUS  
ATTEMPTS TO INQUIRE ABOUT INSPECTION REPORTS BY AN  
ASSOCIATE (D. THOMAS) WERE NOT RESPONDED TO BY THE  
COMPLIANCE DIVISION. MY ASSOCIATE WAS TOLD BY  
COMPLIANCE TO CONTACT THE CSO FOR THE GROUP  
REVIEWING THE DRUG.

15-APR-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: REVIEW REQUEST FOR SUMMARY  
PHARMACOKINETICS PARAMETERS STUDY 906-305  
CONTACT PERSON: SAMARA, EMIL DR. VIA TELEPHONE  
SUMMARY: I CALLED DR. SAMARA TO CLARIFY HIS  
REQUEST FOR MORE INFORMATION FROM STUDY 906-305.  
HE WANTS THE STANDARD ANALYSIS AND SUMMARY  
PHARMACOKINETIC PARAMETERS (TMAX, CMAX, ECT.) TO  
BE PROVIDED. WE WILL PROVIDE THIS FOR HIS REVIEW.  
DR. SAMARA ALSO MENTIONED THE MARKET-IMAGE FOOD  
EFFECT STUDY AND SAID HE WAS SATISFIED WITH THE  
TIME-FRAME FOR SUBMITTING (END OF MONTH).  
FINALLY, DR. SAMARA (REFERRING TO RESPONSE #2 ON  
PROTEIN BINDING) TOOK US UP ON OUR OFFER TO  
PROVIDE SUMMARY DATA. HE INDICATED THIS WAS NOT AN  
APPROVAL ISSUE.

17-APR-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: REQUEST FOR DATA POINTS ON A SLIDE  
PROVIDED TO FDA FOR ACE INHIBITOR  
ADVISORY COMMITTEE MEETING.  
CONTACT PERSON: FENICHEL, R. M.D. VIA TELEPHONE  
SUMMARY: DR. FENICHEL ASKED FOR US TO PROVIDE DATA  
POINTS FOR OUR SLIDE LEK22, PROVIDED TO FDA ON  
APRIL 12, 1991 FOR USE IN THE ADVISORY COMMITTEE  
MEETING IN JUNE. HE WANTS TO CREATE HIS OWN SLIDE  
FOR ILLUSTRATIVE PURPOSES AT THE NEXT PLANNING  
MEETING ON APRIL 19, 1991. I SAID I WOULD FAX THE  
INFORMATION TO HIM TODAY OR EARLY TOMORROW.

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18-APR-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: STATUS OF QUINAPRIL REVIEW.  
CONTACT PERSON: BONGIOVANNI, K. VIA TELEPHONE  
SUMMARY: WHILE SPEAKING TO MS. BONGIOVANNE ABOUT  
ANOTHER TOPIC, I ASKED ABOUT THE STATUS OF THE  
QUINAPRIL REVIEW. SHE SAID THAT AS OF TWO DAYS  
AGO DR. CHEN WAS STILL REVIEWING THE PHARMACOLOGY  
REVIEW OF DR. VAN ARSDEL. SHE DID NOT KNOW IF DR.  
CHEN AND DR. LIPICKY HAD MET TO DISCUSS YET.

19-APR-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: CHECK STATUS OF ACCUPRIL REVIEW  
CONTACT PERSON: CHEN, SHAW DR. VIA IN PERSON  
SUMMARY: I MET WITH DR. CHEN TO DISCUSS THE  
APPROVAL STATUS OF QUINAPRIL. HE SAID THAT HE HAD  
COMPLETED HIS REVIEW OF THE PHARMACOLOGY REVIEW  
(DR. VANARSDEL) AND SENT HIS (DR. CHEN'S REVIEW)  
TO DR. LIPICKY. DRS. CHEN AND LIPICKY WILL MEET IF  
ANY ISSUES ARE APPARENT. I THEN ASKED DR. CHEN FOR  
HIS FEEDBACK ON OUR PROPOSED LABELING. HE HAS  
REVIEWED THE LABELING AND HIS COMMENTS WERE BY-AND-  
-LARGE EDITORIAL, OR ONES THAT COULD BE CONSIDERED  
IN THE REALM OF CLASS LABELING. HE DID WANT US TO  
PROVIDE THE FOLLOWING:  
1) A COPY OF THE LABELING IN LANDSCAPE FORMAT, I.E  
TEXT ON LEFT SIDE BLANK SPACE ON RIGHT SIDE.  
2) IN THE PHARMACODYNAMICS SECTION INCLUDE A  
STATEMENT ABOUT PATIENT WITHDRAWALS, I.E., WHAT  
HAPPENED TO BLOOD PRESSURE?  
CONTINUED - SEE CENTRAL FILE COPY.

23-APR-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: DISCUSS LABELING SUBMISSION FORMAT  
CONTACT PERSON: BONGIOVANNI, K. VIA TELEPHONE  
SUMMARY: I INFORMED MS. BONGIOVANNI THAT WE WERE  
IN THE PROCESS OF RESPONDING TO DE. CHEN'S  
LABELING REQUESTS MADE TO RICH SPIVEY ON 4/19.  
MS. BONGIOVANNI INFORMED ME THAT THEY HAVE NO  
SPECIFIC FORMAT REQUESTS FOR DRAFT LABELING, OTHER  
THAN SUFFICIENT SPACE IN A RIGHT-HAND COLUMN TO  
MAKE COMMENTS AND ADDITIONS. LANDSCAPE VS.  
PORTRAIT WAS NOT A CONCERN. THEY ALSO HAVE NO USE  
FOR WORD PROCESSING DISKS AS DR. TEMPLE WILL MAKE  
HIS COMMENTS DIRECTLY ON THE HARD COPY.  
MS. BONGIOVANNI ASKED WHEN THE LABELING WOULD BE  
SUBMITTED; I REPLIED I WOULD HAND DELIVER IT ON  
THURSDAY. SHE SUGGESTED SUBMITTING BY FAX TO DR.  
CHEN IF WE HAVE IT AVAILABLE EARLY ON WEDNESDAY.  
MS. BONGIOVANNI ALSO NOTED THAT DR. LIPICKY HAS  
DR. CHEN'S REVIEW. HE IS IN ATLANTA UNTIL FRIDAY,  
BUT SHE STILL FEELS THE NDA SHOULD BE TO DR.  
TEMPLE BY THE END OF THE MONTH.

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23-APR-91 MINUTES OF FDA MEETING  
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DATE: 19-APR-91  
PLANNING MEETING FOR JUNE ADVISORY COMMITTEE  
MEETING CARDIOVASCULAR AND RENAL DRUG PRODUCTS.

24-APR-91 42 LETTER RE: REVISED DRAFT LABELING  
CONTENT:

LETTER TO: LIPICKY, RAYMOND M.D.  
RE: REFERENCE IS MADE TO AN APRIL 19, 1991  
CONVERSATION WITH DR. SHAW CHEN, OF YOUR DIVISION,  
CONCERNING LABELING FOR OUR PENDING NDA 19-885,  
ACCUPRIL (QUINAPRIL HYDROCHLORIDE) TABLETS.  
ENCLOSED IS THE REVISED DRAFT LABELING PRESENTED  
IN THE REQUESTED TWO-COLUMN FORMAT. THE FOLLOWING  
CHANGES WERE INSTITUTED:  
PAGE 4  
CLINICAL PHARMACOLOGY:  
ADDED A SENTENCE REGARDING ANTI-HYPERTENSIVE  
EFFECT IN BLACK PATIENTS.  
INDICATIONS AND USAGE:  
ADDED A PARAGRAPH REGARDING AGRANULOCYTOSIS.  
PAGE 5  
WARNINGS:  
ADDED A SENTENCE REGARDING ANGIOEDEMA NOT  
ASSOCIATED WITH ACE INHIBITORS.  
CONTINUED - SEE CENTRAL FILE COPY.

25-APR-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: DELIVER LABELING AND CHECK ON STATUS OF  
REVIEW.  
CONTACT PERSON: CHEN, SHAW DR. VIA IN PERSON  
SUMMARY: I PROVIDED DR. CHEN A DESK COPY OF THE  
LABELING CHANGES WHICH HE HAD REQUESTED LAST WEEK.  
HE NOTED THAT THE FORMAT WAS EXACTLY WHAT HE WAS  
LOOKING FOR.  
I ALSO ASKED DR. CHEN IF THERE WERE ANY CONCERNS  
HE HAD THAT HE HAD TO REVIEW WITH DR. LIPICKY  
PRIOR TO THE NDA GOING TO DR. TEMPLE. DR CHEN  
EXPRESSED FRUSTRATION THAT THE PHARMACOLOGY REVIEW  
WAS SO LATE; HE HAD ISSUES THAT HE NEEDS TO  
DISCUSS WITH DR. LIPICKY THAT SHOULD NOT HAVE HAD  
TO WAIT FOR THE LAST MINUTE. THESE POTENTIAL  
ISSUES WERE RAISED IN THE STATISTICAL REVIEW OF  
THE CARCINOGENICITY STUDIES.  
THE BIOMETRICS REVIEWER QUESTIONED WHETHER THE  
DOSES USED THE MOUSE STUDY WERE HIGH ENOUGH IN  
THAT LITTLE TOXICITY WAS SEEN OTHER THAN WEIGHT  
LOSS. CONTINUED - SEE CENTRAL FILE COPY.

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25-APR-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: STATUS OF REVIEWS AND DELIVER DESK COPIES  
CONTACT PERSON: BONGIOVANNI, K. VIA IN PERSON  
SUMMARY: I PROVIDED MS. BONGIOVANNI WITH DESK  
COPIES OF THE NEW LABELING FOR QUINAPRIL AND THE  
SAFETY UPDATE FOR ACCURETIC.  
MS. BONGIOVANNI NOTED THAT THIS WOULD BE A GOOD  
TIME TO SUBMIT THE FINAL PRINTED LABELS FOR  
CARTONS AND CONTAINERS. SHE ALSO ASKED ABOUT THE  
STATUS OF OUR ADVERTISING. I NOTED THAT WE HOPED  
TO PROVIDE IT TO THE DRUG ADVERTISING DIVISION  
SHORTLY, BUT THOUGHT THAT THAT WAS NOT CRITICAL  
FOR APPROVAL. MS. BONGIOVANNI AGREED THAT,  
TECHNICALLY, THE ADVERTISING IS "REQUESTED" AND  
NOT REQUIRED FOR APPROVAL, BUT ALSO NOTED THAT DR.  
TEMPLE HAS BEEN KNOWN TO HOLD APPROVALS UNTIL  
SOMEONE IN THE REVIEW DIVISION HAS REVIEWED THE  
LAUNCH PROMOTINAL MATERIALS.  
I NOTED WE WOULD BE SURE TO SUBMIT THESE MATERIALS  
WITHIN A COUPLE OF WEEKS.  
CONTINUED - SEE CENTRAL FILE COPY.

25-APR-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: RAT BIOASSAY STUDY  
CONTACT PERSON: CHEN, SHAW DR. VIA TELEPHONE  
ABSTRACT: DR. CHEN REQUESTED CONFIRMATION THAT  
SLIDES FROM THE RAT BIOASSAY STUDY WERE READ IN A  
BLINDED FASHION. WE SHOULD INDICATE WHERE IN THE  
NDA SUCH STATEMENT EXISTS OR PROVIDE SUCH A  
STATEMENT IN WRITING IF THAT IS CORRECT.

25-APR-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: FDA BIOMETRICS REVIEW  
CONTACT PERSON: LIPICKY, RAY DR. VIA IN PERSON  
ABSTRACT: CONCERNED OVER FDA BIOMETRICS REVIEW  
OF CARCINOGENICITY STUDIES.

26-APR-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: REQUEST LOCATION OF DESCRIPTION OF  
BLINDING REGIMEN IN CARCINOGENICITY  
STUDIES.  
CONTACT PERSON: BONGIOVANNI, K. VIA TELEPHONE  
ABSTRACT: REQUEST LOCATION OF DESCRIPTION OF  
BLINDING REGIMEN IN CARCINOGENICITY STUDIES.

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26-APR-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: FOLLOW-UP TO 4/25 VIST AND CONVERSATION  
WITH DR. LIPICKY.  
CONTACT PERSON: CHEN, SHAW DR. VIA TELEPHONE  
ABSTRACT: FOLLOW-UP TO 4/25 VISIT AND CONVERSATION  
WITH DR. LIPICKY.

29-APR-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: CONFIRM RESOLUTION OF ISSUE RAISED BY  
DR. LIPICKY ON 4/25.  
CONTACT PERSON: CHEN, SHAW DR. VIA TELEPHONE  
ABSTRACT: CONFIRM RESOLUTION OF ISSUE RAISED BY  
DR. LIPICKY ON 4/25.

29-APR-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: REQUEST ADDITIONS TO QUINAPRIL LABELING  
CONTACT PERSON: CHEN, SHAW DR. VIA TELEPHONE  
ABSTRACT: REQUEST ADDITIONS TO QUINAPRIL LABELING.

30-APR-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: QUESTIONS ON SBA PAGES 76 AND 78.  
CONTACT PERSON: CHEN, SHAW DR. VIA TELEPHONE  
MEMO FROM: SPIVEY, R.  
SUMMARY: DR. CHEN CALLED TO CLARIFY THE GRAPHS  
GIVEN ON P. 76 AND 78 OF THE SBA. OUR MOST RECENT  
UPDATES OF THESE TWO PAGES HAVE SWITCHED THE  
GRAPHS, I.E. FIGURE 15 ON PAGE 76 SHOULD BE ON  
PAGE 78 AND VICE VERSA. NOTE THAT THE FIGURE  
TITLES ARE CORRECT, THE FIGURES HAVE BEEN  
TRANSPOSED. I AGREED TO SEND HIM CORRECTED PAGES.

01-MAY-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: STATUS OF LAST MINUTE ITEMS BEFORE NDA  
GOES TO DR. TEMPLE.  
CONTACT PERSON: BONGIOVANNI, K. VIA IN PERSON  
MEMO FROM: MARTIN, IRWIN  
ABSTRACT: DESCRIPTION OF CARCINOGENICITY STUDY  
BLINDING PROCEDURE ONLY OUTSTANDING ITEM.

01-MAY-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: ACCUPRIL NDA SUPPLEMENTS  
CONTACT PERSON: CUNNINGHAM, D. VIA IN PERSON  
MEMO FROM: BRENNAN, S  
ABSTRACT: CONTENT OF ACCUPRIL NDA SUPPLEMENTS FOR  
40-MG TABLET AND TECH TRANSFER DISCUSSED.



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01-MAY-91 43 LETTER RE: REVISED LABELING  
CONTENT:

LETTER TO: LIPICKY, RAYMOND M.D.  
LETTER FROM: MARTIN, IRWIN  
RE: WE ARE RESPONDING TO AN APRIL 29, 1991 REQUEST  
FROM DR. SHAW CHEN, OF YOUR DIVISION, CONCERNING  
OUR PENDING NDA 19-885 FOR QCCUPRIL (QUINAPRIL  
HYDROCHLORIDE) TABLETS. DR. CHEN REQUESTED THAT WE  
PROVIDE ADDITIONAL WORDING IN THE PRECAUTIONS  
SECTION ADDRESSING USE OF ACCUPRIL IN GERIATRIC  
PATIENTS. ATTACHED IS A REVISED LABELING PAGE WITH  
THE REQUESTED NEW INFORMATION. THIS PAGE REPLACES  
PAGE 12 OF OUR SUBMISSION OF APRIL 24, 1991  
(REF. NO. 42).  
SEE ATTACHEMENTS

02-MAY-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: COMPLIANCE INSPECTION REPORT FOR  
ACCUPRIL.  
CONTACT PERSON: CUNNINGHAM, D. MS VIA TELEPHONE  
MEMO FROM: BRENNAN, S.  
ABSTRACT: COMPLIANCE INSPECTION REPORT FOR  
ACCUPRIL RECEIVED BY DIVISION OF CARDIO-RENAL.

02-MAY-91 44 LETTER RE: SBA; RAT CARCINOGENICITY REPORT  
CONTENT:

LETTER TO: LIPICKY, RAYMOND M.D.  
LETTER FROM: MARTIN, IRWIN  
RE: WE ARE RESPONDING TO AN APRIL 30, 1991 REQUEST  
FROM DR. SHAW CHEN, OF YOUR DIVISION, CONCERNING  
THE DRAFT SUMMARY BASIS OF APPROVAL (SBA) OF OUR  
PENDING NDA FOR ACCUPRIL (QUINAPRIL HYDROCHLORIDE)  
TABLETS. DR. CHEN ASKED THAT WE PROVIDE CORRECTED  
FIGURES FOR FIGURE 15 (PAGE 76) AND FIGURE 17  
(PAGE 78) OF THE DRAFT SBA. WE HAVE PROVIDED, IN  
ATTACHEMENT 1, REPLACEMENT PAGES 76 AND 78 FOR THE  
SBA, SUBMITTED OCTOBER 31, 1991, (REF. NO. 18) AND  
REVISED NOVEMBER 27, 1990 (REF. NO. 24).  
WE ARE ALSO PROVIDING IN ATTACHMENT 2, PER A MAY  
1, 1991 REQUEST COMMUNICATED BY MS. KATHLEEN  
BONGIOVANNI OF YOUR DIVISION, A SUMMARY OF THE  
PROCEDURE USED BY A PEER REVIEW PANEL OF EXPERT  
PATHOLOGISTS TO EVALUATE HISTOLOGY SLIDES FROM THE  
RAT CARCINOGENICITY STUDY (RR 745-01173, VOL 20,  
P. 002431, JAN 26, 1989).  
CONTINUED - SEE CENTRAL FILE COPY.

03-MAY-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: FOLLOW-UP TO 5/1 REQUEST ON  
CARCINOGENICITY STUDY SLIDE BLINDING.  
CONTACT PERSON: BONGIOVANNI, K. VIA TELEPHONE  
MEMO FROM: MARTIN, IRWIN  
ABSTRACT: FOLLOW-UP TO 5/1 REQUEST ON  
CARCINOGENICITY STUDY SLIDE BLINDING.

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CONTENT:

FDA CONTACT MEMO

MEMO RE: DETERMINE STATUS OF FOSENAPRIL NDA;  
DETERMINE STATUS OF LIPICKY QUINAPRIL  
REVIEW.

CONTACT PERSON: BONGIOVANNI, K. VIA TELEPHONE  
MEMO FROM: MARTIN, IRWIN  
ABSTRACT: DETERMINE STATUS OF FOSENAPRIL NDA;  
DETERMINE STATUS OF LIPICKY QUINAPRIL REVIEW.

07-MAY-91  
CONTENT:

FDA CONTACT MEMO

MEMO RE: FOLLOW-UP TO APRIL 15 CONTACT RE:  
BIOPHARM REVIEW OF 906-305.  
CONTACT PERSON: CHEN, SHAW DR. VIA TELEPHONE  
MEMO FROM: MARTIN, I.  
ABSTRACT: FOLLOW-UP TO APRIL 15 CONTACT RE:  
BIOPHARM REVIEW OF 906-305.

08-MAY-91  
CONTENT:

FDA CONTACT MEMO

MEMO RE: STATUS OF QUINAPRIL NDA REVIEW  
CONTACT PERSON: BONGIOVANNI, K. VIA IN PERSON  
MEMO FROM: MARTIN, I.  
ABSTRACT: THE QUINAPRIL NDA IS LIKELY TO BE TO DR.  
TEMPLE ON FRIDAY, MAY 10.  
JUNE 6/7 ADVISORY COMMITTEE TOPIC CHANGED; WILL NO  
LONGER BE ABOUT ACES (SEE ATTACHED).

10-MAY-91  
CONTENT:

FDA CONTACT MEMO

MEMO RE: STATUS OF NDA  
CONTACT PERSON: BONGIOVANNI, K. VIA IN PERSON  
MEMO FROM: MARTIN, I.  
ABSTRACT: NDA TO DR. TEMPLE 5/10 OR 5/13.

13-MAY-91  
CONTENT:

FDA CONTACT MEMO

MEMO RE: STATUS OF NDA  
CONTACT PERSON: BONGIOVANNI, K. VIA IN PERSON  
MEMO FROM: MARTIN, I.  
ABSTRACT: NDA SENT TO DR. TEMPLE.

14-MAY-91  
CONTENT:

FDA CONTACT MEMO

MEMO RE: DRAFT AGENDA FOR JUNE 6-7 ADVISORY  
COMMITTEE.  
CONTACT PERSON: BONGIOVANNI, K VIA TELEPHONE  
MEMO FROM: MARTIN, I.  
ABSTRACT: DRAFT AGENDA FOR JUNE 6-7 ADVISORY  
COMMITTEE.

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20-MAY-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: HOW TO SUBMIT "FOOD-EFFECT" STUDY.  
CONTACT PERSON: BONGIOVANNI, D. VIA TELEPHONE  
MEMO FROM: MARTIN, I.  
ABSTRACT: DISCUSSION OF SUBMISSION OF "FOOD-EFFECT" STUDY.

23-MAY-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: REQUEST SLIDES FOR OCTOBER CARDIO-RENAL  
ADVISORY COMMITTEE MEETING.  
CONTACT PERSON: BONGIOVANNI, K.  
MEMO FROM: SPIVEY, R.  
ABSTRACT: REQUEST SLIDES FOR OCTOBER CARDIO-RENAL  
ADVISORY COMMITTEE MEETING.

24-MAY-91 45 LETTER RE: GENERAL CORRESPONDENCE  
CONTENT:

LETTER TO: LIPICKY, RAYMOND M.D.  
LETTER FROM: MARTIN, IRWIN  
RE: REFERENCE IS MADE TO OUR PENDING NDA 19-885  
FOR ACCUPRIL (QUINAPRIL HYDROCHLORIDE) TABLETS. AS  
NOTED IN OUR SUBMISSION OF APRIL 11, 1991 (REF. NO  
41), WE ARE PROVIDING THE REPORT OF STUDY 906-369,  
A STUDY OF THE EFFECT OF A HIGH FAT MEAL ON THE  
BIOAVAILABILITY OF QUINAPRIL MARKET-IMAGE TABLETS.  
THE FINDINGS FROM THIS STUDY ARE NOT IN AGREEMENT  
WITH THOSE SUBMITTED IN OUR ORIGINAL NDA. WE ARE,  
THEREFORE, PROPOSING THAT THE FOLLOWING  
CHANGES BE MADE TO THE DRAFT LABELING FOR  
ACCUPRIL.  
CONTINUED - SEE CENTRAL FILE COPY.

28-MAY-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: DISCUSS SUBMISSION STRATEGY FOR FOOD  
EFFECT STUDY.  
CONTACT PERSON: ROEDER, DAVID VIA IN PERSON  
MEMO FROM: MARTIN, I.  
ABSTRACT: DISCUSS SUBMISSION STRATEGY FOR FOOD  
EFFECT STUDY.

29-MAY-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: FOLLOW-UP TO 5/28 CONVERSATION.  
CONTACT PERSON: ROEDER, DAVID VIA IN PERSON  
MEMO FROM: MARTIN, I.  
ABSTRACT: DR. TEMPLE DID NOT THINK THE FOOD EFFECT  
STUDY WOULD SLOW DOWN THE NDA APPROVAL.

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30-MAY-91		FDA CONTACT MEMO
CONTENT:		
MEMO RE: QUESTION ON FOOD EFFECT STUDY.		
CONTACT PERSON: SAMARA, EMIL VIA TELEPHONE		
MEMO FROM: MARTIN, I.		
ABSTRACT: QUESTION ON FOOD EFFECT STUDY.		
31-MAY-91		FDA CONTACT MEMO
CONTENT:		
MEMO RE: DETERMINE WHETHER WE CAN SUBMIT LAUNCH		
MATERIALS PRIOR TO RECEIPT OF APPROVABLE		
LETTER.		
CONTACT PERSON: KNIPPEN, M. VIA TELEPHONE		
MEMO FROM: SPIVEY, R.		
ABSTRACT: DETERMINE WHETHER WE CAN SUBMIT LAUNCH		
MATERIALS PRIOR TO RECEIPT OF APPROVABLE LETTER.		
31-MAY-91		FDA CONTACT MEMO
CONTENT:		
MEMO RE: NDA UPDATE.		
CONTACT PERSON: ROEDER, DAVID		
MEMO FROM: MARTIN, I.		
ABSTRACT: NDA UPDATE.		
31-MAY-91		FDA CONTACT MEMO
CONTENT:		
MEMO RE: FOLLOW-UP TO 5/30 TELEPHONE CALL.		
CONTACT PERSON: SAMARA, EMIL		
MEMO FROM: MARTIN, I.		
ABSTRACT:		
- CONFIRMATORY CALCULATIONS PROVIDED TO DR. SAMARA		
- DR. SAMARA HAS COMPLETED REVIEW OF FOOD EFFECT		
STUDY.		
- MINOR QUESTIONS ON METHODOLOGY RECEIVED; NOT		
APPROVAL-RELATED.		
05-JUN-91		FDA CONTACT MEMO
CONTENT:		
MEMO RE: STATUS OF TEMPLE'S NDA REVIEW.		
CONTACT PERSON: ROEDER, DAVID VIA TELEPHONE		
MEMO FROM: MARTIN, I.		
ABSTRACT: DR. TEMPLE HAD NOT YET BEGUN HIS REVIEW.		
07-JUN-91		FDA CONTACT MEMO
CONTENT:		
MEMO RE: DRUG PRODUCT MANUFACTURING SITES FOR NDAS		
CONTACT PERSON: ZOSCHNICK, M. VIA TELEPHONE		
MEMO FROM: BRENNAN, S.		
SUMMARY: MR. ZOSCHNICK CALLED REGARDING THE DRUG		
PRODUCT MANUFACTURING SITES FOR SIX OF OUR PENDING		
NDAS. HE EXPLAINED THAT THE DETROIT OFFICE		
RECEIVED A LIST OF SIX NDAS FROM THE WASHINGTON		

COMPLIANCE OFFICE WHICH COULD BE APPROVED IN THE  
NEXT 12 MONTHS. THESE APPLICATIONS WERE:  
SEE MEMO.

I ASKED HIM IF HE WAS INTERESTED IN THE DRUG  
SUBSTANCE MANUFACTURING SITES BECAUSE MOST OF THE  
DRUG PRODUCTS HE INQUIRED ABOUT WERE MANUFACTURED  
OUTSIDE THE DETROIT DISTRICT. HE SAID HIS PRIMARY  
INTEREST WAS DRUG PRODUCT MANUFACTURING SITES.  
IN RESPONSE TO HIS REQUEST, THE ATTACHED SUMMARY  
TABLES WERE SENT TO HIM BY TELECOPY. THE TABLES  
SUMMARIZE THE MANUFACTURING AND PACKAGING SITES  
LISTED IN OUR PENDING NDAS.

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24-JUN-91 FDA CONTACT MEMO

CONTENT:

MEMO RE: NDA STATUS  
CONTACT PERSON: BONGIOVANNI, D. VIA TELEPHONE  
MEMO FROM: MARTIN, I.  
ABSTRACT: NDA STATUS.

27-JUN-91 LETTER RE: ANNUAL REPORT

CONTENT:

LETTER TO: SCHALL, THOMAS  
LETTER FROM: SPIVEY, RICHARD  
RE: IN ACCORDANCE WITH THE DRUG EXPORT AMENDMENTS  
ACT OF 1986, WE ARE PROVIDING A SUMMARY OF ACTIONS  
TAKEN BY PARKE-DAVIS/WARNER-LAMBERT IN PURSUIT OF  
MARKETING APPROVAL OF QUINAPRIL DURING THE PAST  
YEAR. PLEASE REFER TO OUR DRUG EXPORT APPLICATIONS  
END-0058, END-0058A01 AND END-0058A02.  
THE NEW DRUG APPLICATION FOR QUINAPRIL (NDA 19-  
885) WAS SUBMITTED TO THE FOOD AND DRUG ADMINIS-  
TRATION ON 26-JAN-89. THE APPLICATION IS CURRENTLY  
UNDER ACTIVE REVIEW BY THE DIVISION OF CARDIO-  
RENAL DRUG PRODUCTS, OFFICE OF DRUG EVALUATION I.  
IN THIS REPORTING PERIOD PARKE-DAVIS HAS SUBMITTED  
DRAFTS OF THE SUMMARY BASIS OF APPROVAL, TWO ADD-  
ITIONAL SAFETY UPDATES AND REVISIONS OF THE PRO-  
POSED LABELING WITH SUPPORTING DOCUMENTATION.  
WE BELIEVE THAT THE ABOVE INFORMATION SEVERS TO  
DOCUMENT OUR ACTIVE PURSUIT OF APPROVAL OF THE  
QUINAPRIL NEW DRUG APPLICATION.

02-JUL-91 FDA CONTACT MEMO

CONTENT:

MEMO RE: FOLLOW-UP TO TELEPHONE MESSAGES OF 6/27  
AND 6/28.  
CONTACT PERSON: BONGIOVANNI, K. VIA IN PERSON  
MEMO FROM: MARTIN, I.  
ABSTRACT: FOLLOW-UP TO TELEPHONE MESSAGES OF 6/27  
AND 6/28.

10-JUL-91 FDA CONTACT MEMO

CONTENT:

MEMO RE: FOLLOW-UP TO REQUEST OF 7/2; STATUS OF  
NDA REVIEWS.  
CONTACT PERSON: BONGIOVANNI, K. VIA IN PERSON  
MEMO FROM: MARTIN, I.  
ABSTRACT: FOLLOW-UP TO REQUEST OF 7/2; STATUS OF  
NDA REVIEWS.

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16-JUL-91		FDA CONTACT MEMO
CONTENT:		MEMO RE: FOLLOW-UP TO 7/15 MEETING; INFORM OF MERINO DISCUSSION WITH TEMPLE. CONTACT PERSON: BONGIOVANNI, K. VIA TELEPHONE ABSTRACT: NDA TO GP TO CAC PER DR. TEMPLE, BUT NOT NECESSARILY PRIOR TO APPROVAL.
16-JUL-91		FDA CONTACT MEMO
CONTENT:		MEMO RE: FOLLOW-UP TO REQUEST FOR INFORMATION ON 5-31-91. CONTACT PERSON: SAMARA, E. DR. VIA TELEPHONE MEMO FROM: SPIVEY, R. ABSTRACT: FOLLOW-UP TO REQUEST FOR INFORMATION ON 5-31-91.
18-JUL-91		FDA CONTACT MEMO
CONTENT:		MEMO RE: ADDITIONAL QUESTIONS ON 2-YEAR RAT CARCINOGENICITY STUDY. CONTACT PERSON: VANARSDEL, W. VIA TELEPHONE MEMO FROM: MARTIN, I. ABSTRACT: ADDITIONAL QUESTIONS ON 2-YEAR RAT CARCINOGENICITY STUDY.
30-JUL-91		FDA CONTACT MEMO
CONTENT:		MEMO RE: FOLLOW-UP TO QUESTIONS REGARDING 2-YEAR RAT CARCINOGENICITY STUDY (SEE JULY 18). CONTACT PERSON: VAN ARSDEL, W. VIA TELEPHONE MEMO FROM: SPIVEY, R. ABSTRACT: FOLLOW-UP TO QUESTIONS REGARDING 2-YEAR RAT CARCINOGENICITY STUDY (SEE JULY 18).
31-JUL-91		FDA CONTACT MEMO
CONTENT:		MEMO RE: STATUS OF NDA REVIEW. CONTACT PERSON: BONGIOVANNI, K. VIA IN PERSON MEMO FROM: MARTIN, I. ABSTRACT: STATUS OF NDA REVIEW.
02-AUG-91		FDA CONTACT MEMO
CONTENT:		MEMO RE: FOLLOW-UP TO 7/13 VISIT. CONTACT PERSON: BONGIOVANNI, K. VIA TELEPHONE MEMO FROM: MARTIN, I. ABSTRACT: CAC SCHEDULED FOR 8/16; DEFELICE TO CALL TO DISCUSS VANARSDEL REQUEST.

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CONTENT:

FDA CONTACT MEMO

MEMO RE: CONFIRM FDA'S RECEIPT OF GLP INSPECTION  
REPORT.  
CONTACT PERSON: BONGIOVANNI, K. VIA TELEPHONE  
MEMO FROM: SPIVEY, R.  
ABSTRACT: CONFIRM FDA'S RECEIPT OF GLP INSPECTION  
REPORT.

06-AUG-91  
CONTENT:

FDA CONTACT MEMO

MEMO RE: UPDATE ON NDA STATUS.  
CONTACT PERSON: BONGIOVANNI, K.  
MEMO FROM: MARTIN, I.  
ABSTRACT: MS. BONGIOVANNI INFORMED THAT DR.  
TEMPLE'S REVIEW IS NEARING COMPLETION.

12-AUG-91  
CONTENT:

FDA CONTACT MEMO

MEMO RE: TO DISCUSS THE STATUS OF THE QUINAPRIL  
NDA.  
CONTACT PERSON: TEMPLE, ROBERT DR. VIA TELEPHONE  
MEMO FROM: MERINO, WILLIAM  
ABSTRACT: TWO REMAINING ISSUES WERE DISCUSSED, ONE  
WAS RESOLVED AND THE OTHER CAN BE RESOLVED AFTER  
RECEIPT OF THE APPROVABLE LETTER.

14-AUG-91  
CONTENT:

FDA CONTACT MEMO

MEMO RE: UPDATE ON NDA ISSUES.  
CONTACT PERSON: BONGIOVANNI, K. VIA IN PERSON  
MEMO FROM: MARTIN, I.  
ABSTRACT: QUINAPRIL TO BE DISCUSSED 8/15 AT  
C.A.C.; APPROVABLE LETTER TO FOLLOW SHORTLY  
THEREAFTER.

14-AUG-91  
CONTENT:

FDA CONTACT MEMO

MEMO RE: DISCUSS 40 MG TABLET SNDA.  
CONTACT PERSON: WOLTERS, R. VIA IN PERSON  
MEMO FROM: MARTIN, I.  
ABSTRACT: DR. WOLTERS OFFERED SUGGESTIONS FOR 40  
MG TABLET SNDA.

15-AUG-91  
CONTENT:

FDA CONTACT MEMO

MEMO RE: RECEIPT OF APPROVABLE LETTER.  
CONTACT PERSON: BONGIOVANNI, K. VIA TELEPHONE  
MEMO FROM: MARTIN, I.  
ABSTRACT: APPROVABLE LETTER RECEIVED.



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15-AUG-91 FDA CONTACT MEMO

CONTENT:

MEMO RE: FEEDBACK ON CAC MEETING.  
CONTACT PERSON: BONGIOVANNI, K. VIA TELEPHONE  
MEMO FROM: MARTIN, I.  
ABSTRACT: CAC DECIDED RAT BIOASSAY WAS ACCEPTABLE;  
MOUSE BIOASSAY ACCEPTABLE ONLY IF SEVERITY OF  
NEPHRITIS INCREASED WITH DOSE. POST-APPROVAL  
ANALYSES BY SEX WILL BE REQUESTED FOR THE SBA.

15-AUG-91 FDA CONTACT MEMO

CONTENT:

MEMO ER: QUESTIONS DURING CAC MEETING.  
CONTACT PERSON: CHEN, S. DR. VIA TELEPHONE  
MEMO FROM: MARTIN, I.  
ABSTRACT: QUESTIONS ON SEX DIFFERENCES OF  
QUINAPRIL ACTION.

15-AUG-91 LETTER RE: FINAL PRINTED LABELING FOR DRUG

CONTENT:

LETTER TO: MARTIN, I.  
LETTER FROM: TEMPLE, ROBERT M.D.  
RE: PLEASE REFER TO YOUR 26-JAN-89 NDA SUBMITTED  
UNDER SECTION 505(B) OF THE FEDERAL FOOD, DRUG,  
AND COSMETIC ACT FOR ACCUPRIL (QUINAPRIL HCL) TAB.  
WE ALSO ACKNOWLEDGE RECEIPT OF YOUR AMENDMENTS AND  
CORRESPONDENCE DATED FROM 23-MAY-89 THROUGH  
02-MAY-91. (SEE FILE COPY FOR COMPLETE DATES)  
WE HAVE COMPLETED THE REVIEW OF THIS APPLICATION  
AS SUBMITTED WITH DRAFT LABELING. BEFORE THE  
APPLICATION MAY BE APPROVED, HOWEVER, IT WILL BE  
NECESSARY FOR YOU TO SUBMIT FINAL PRINTED LABELING  
FOR THE DRUG. THE LABELING SHOULD BE IDENTICAL IN  
CONTENT TO THE ENCLOSED MARKED-UP DRAFT. IF  
ADDITIONAL INFORMATION RELATING TO THE SAFETY OR  
EFFECTIVENESS OF THIS DRUG BECOMES AVAILABLE  
BEFORE WE RECEIVE THE FINAL PRINTED LABELING,  
REVISION OF THAT LABELING MAY BE REQUIRED.  
CONTINUED - SEE CENTRAL FILE COPY.

16-AUG-91 FDA CONTACT MEMO

CONTENT:

MEMO RE: CHANGE IN LABELING MEETING.  
CONTACT PERSON: BONGIOVANNI, K. VIA TELEPHONE  
MEMO FROM: MARTIN, I.  
ABSTRACT: LABELING NEGOTIATIONS MEETING CHANGED TO  
22-AUG-91.

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16-AUG-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: FOLLOW-UP TO CAC(2).  
CONTACT PERSON: BONGIOVANNI, K.  
MEMO FROM: MARTIN, I.  
ABSTRACT: RODENT HEMATOLOGY AND CLINICAL CHEMISTRY  
DATA REQUESTED.

20-AUG-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: QUESTIONS ON APPROVABLE LETTER LABELING  
AND PROPOSED CHANGES.  
CONTACT PERSON: DEFELICE, A. PH.D. VIA TELEPHONE  
MEMO FROM: MARTIN, I.  
ABSTRACT: MINOR CHANGES AGREED TO IN LABELING.  
SUMMARY OF MOUSE DATA REQUESTED TO COMPLETE  
QUINAPRIL FILE.

20-AUG-91 46 LETTER RE: LABELING  
CONTENT:

LETTER TO: LIPICKY, RAYMOND M.D.  
LETTER FROM: MARTIN, I.  
RE: REFERENCE IS MADE TO OUR PENDING NDA FOR  
ACCUPRIL (QUINAPRIL HYDROCHLORIDE) TABLETS, NDA  
19-885, SUBMITTED 26-JAN-89. ADDITIONAL REFERENCE  
IS MADE TO THE 15-AUG-91 APPROVABLE LETTER FOR  
ACCUPRIL FROM DR. TEMPLE. FURTHER REFERENCE IS  
MADE TO THE UPCOMING MEETING BETWEEN PARKE-DAVIS  
AND DR. TEMPLE, DR. DEFELICE AND DR. CHEN  
SCHEDULED FOR THURSDAY, 22-AUG AT 4 PM. THE  
PURPOSE OF THIS MEETING IS TO FINALIZE THE  
LABELING FOR ACCUPRIL TABLETS.  
ATTACHED ARE OUR PROPOSED REVISIONS TO THE  
LABELING. THE CHANGES AS PROPOSED BY THE AGENCY  
HAVE BEEN INCORPORATED INTO THE TYPED MANUSCRIPT  
IN THE LEFT COLUMN OF THE ATTACHMENT; THE NEW  
PARKE-DAVIS PROPOSALS ARE CONTAINED IN THE RIGHT  
COLUMN.  
CONTINUED - SEE FILE COPY.

21-AUG-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: CONFIRM RECEIPT OF LABELING.  
CONTACT PERSON: BENTON, SANDY VIA TELEPHONE  
MEMO FROM: MARTIN, I.  
ABSTRACT: PROPOSED FINAL LABELING RECEIVED.

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21-AUG-91 47 LETTER RE: OCCURRENCE OF NEPHROPATHY  
CONTENT:

LETTER TO: DEFELICE, ALBERT PH.D.  
LETTER FROM: MARTIN, IRWIN PH.D.  
RE: REFERENCE IS MADE TO OUR 15-AUG-91 TELEPHONE  
CONVERSATION REGARDING THE OCCURRENCE OF  
NEPHROPATHY IN THE MOUSE BIOASSAY FOR QUINAPRIL  
(NDA 19-885). YOU INDICATED THAT THE  
CARCINOGENICITY ASSESSMENT COMMITTEE INQUIRED  
WHETHER THERE WAS AND INCREASE IN SEVERITY OF  
NEPHROPATHY CORRESPONDING TO AN INCREASE IN DOSE.  
KIDNEYS FROM ALL MICE IN THE QUINAPRIL TUMOR  
BIOASSAY WERE EVALUATED HISTOPATHOLOGICALLY BY A  
CONSULANT. THE CONSULANT'S REPORT IS ATTACHED  
(RR 745-01450 PP. 37-59). A GRADING SYSTEM WAS  
USED TO RANK THE SEVERITY OF CHRONIC NEPHROPATHY,  
WHICH RANGED FROM GRADE 1 (MINIMAL) TO GRADE 5  
(END-STAGE). RESULTS SHOW THAT SEVERITY OF  
SPONTANEOUS NEPHROPATHY WAS INCREASED IN FEMALES  
AT 35 AND 75 MG/KG AND IN MALES AT 75 MG/KG.  
THIS RESEARCH REPORT WAS SUBMITTED TO OUR NDA  
19-885 ON 26-MAY-89. QUESTIONS CALL-----

22-AUG-91 50 LETTER RE: TABLES OF SAFETY INFORMATION  
CONTENT:

LETTER TO: LIPICKY, RAYMOND M.D.  
LETTER FROM: MARTIN, I.  
RE: REFERENCE IS MADE TO OUR PENDING NDA FOR  
ACCUPRIL (QUINAPRIL HYDROCHLORIDE) TABLETS, NDA  
19-885. ADDITIONAL REFERENCE IS MADE TO OUR SUB-  
MISSION OF PROPOSED FINAL LABELING ON 20-AUG-91.  
ENCLOSED PLEASE FIND THE SUMMARY TABLES OF SAFETY  
INFORMATION FROM THE QUINAPRIL SAFETY DATABASE  
UPON WHICH THE REVISED ADVERSE REACTIONS SECTION  
OF THE LABELING WAS BASED.

23-AUG-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: FOLLOW-UP TO 8/22 MEETING.  
CONTACT PERSON: BONGIOVANNI, K. VIA TELEPHONE  
MEMO FROM: MARTIN, I.  
ABSTRACT: FINAL SUBMISSION TO PENDING NDA  
REVIEWED.

23-AUG-91 MINUTES OF FDA MEETING  
CONTENT:

DATE: 22-AUG-91  
FDA MEETING RE: ACCUPRIL LABELING .

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26-AUG-91  
CONTENT:

LETTER RE: JOURNAL ADVERTISEMENT, AND SALES VISUAL AID

LETTER TO: WITT, ANN (SEE REF #49 FOR ATTACHMENTS)  
LETTER FROM: MARTIN, I.  
RE: REFERENCE IS MADE TO OUR PENDING NDA 19-885  
FOR ACCUPRIL (QUINAPRIL HCL) TABLETS. WE HAVE  
ENCLOSED, FOR YOUR REVIEW, OUR PROPOSED 8-PAGE  
JOURNAL ADVERTISEMENT AND SALES VISUAL AID, USED  
IN THE INITIAL PROMOTIONAL CAMPAIGN FOR ACCUPRIL.  
UNDER SEPARATE COVER THESE MATERIALS HAVE ALSO  
BEEN FORWARDED TO THE DIVISION OF CARDIO-RENAL  
DRUG PRODUCTS.  
ALSO ENCLOSED IS OUR FINAL PRINTED LABELING WHICH  
INCLUDES AGREED-UPON CHANGES FROM OUR MEETING WITH  
DR. TEMPLE ON 22-AUG. THIS LABELING WAS SUBMITTED  
AUG-26-91.  
QUESTIONS-----

26-AUG-91  
CONTENT:

48 LETTER RE: FINAL PRINTED LABELING

LETTER TO: LIPICKY, RAYMOND M.D.  
LETTER FROM: MARTIN, IRWIN  
RE: REFERENCE IS MADE TO OUR PENDING NDA FOR  
ACCUPRIL (QUINAPRIL HCL) TABLETS, NDA 19-885,  
SUBMITTED 26-JAN-89. ADDITIONAL REFERENCE IS MADE  
TO THE 15-AUG-91 APPROVABLE LETTER FOR ACCUPRIL  
FROM DR. TEMPLE. FURTHER REFERENCE IS MADE TO THE  
MEETING BETWEEN PARKE-DAVIS AND AGENCY  
REPRESENTATIVES ON 22-AUG-91.  
AS AGREED AT THE ABOVE-REFERENCED MEETING, WE ARE  
SUBMITTING FINAL PRINTED LABELING WHICH IS  
IDENTICAL TO THE DRAFT LABELING SUBMITTED ON  
20-AUG-91 (NDA REF 46) WITH THE CHANGES AGREED TO  
AT THE 22-AUG-91 MEETING. A DESCRIPTION OF THESE  
CHANGES IMMEDIATELY FOLLOWS THIS COVER LETTER.  
APPENDICES 1-3 INCLUDE FINAL PRINTED CARTON AND  
CONTAINER LABELS WHICH ARE IDENTICAL TO THOSE  
INCLUDED IN DRAFT FORM IN THE ORIGINAL NDA.  
WE WILL NOT MARKET ACCUPRIL UNTIL WE HAVE RECEIVED  
WRITTEN APPROVAL.

26-AUG-91  
CONTENT:

49 LETTER RE: INITIAL ADVERTISING CAMPAIGN

LETTER TO: LIPICKY, RAYMOND  
LETTER FROM: MARTIN, I.  
RE: REFERENCE IS MADE TO OUR PENDING NDA 19-885  
FOR ACCUPRIL (QUINAPRIL HCL) TABLETS. WE HAVE  
ENCLOSED, FOR YOUR REVIEW, OUR PROPOSED 8-PAGE  
JOURNAL ADVERTISEMENT AND SALES FORCE VISUAL AID  
TO BE USED IN THE INITIAL ADVERTISING CAMPAIGN  
FOR ACCUPRIL. UNDER SEPARATE COVER THESE MATERIALS  
HAVE ALSO BEEN FORWARDED TO THE DIVISION OF  
MARKETING, ADVERTISING AND COMMUNICATIONS.  
ALSO ENCLOSED IS OUR FINAL PRINTED LABELING WHICH  
INCLUDES AGREED-UPON CHANGES FROM OUR MEETING WITH  
DR. TEMPLE ON 22-AUG. THIS LABELING WAS SUBMITTED  
26-AUG-91.  
QUESTIONS-----

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27-AUG-91		FDA CONTACT MEMO
CONTENT:		MEMO RE: FOLLOW-UP TO LABELING SUBMISSION OF 8/26. CONTACT PERSON: BONGIOVANNI, K. VIA TELEPHONE MEMO FROM: MARTIN, I. ABSTRACT: MS. BONGIOVANNI HAD ONE ADDITION TO FPL; IT WILL NOT SLOW DOWN APPROVAL.
27-AUG-91		FDA CONTACT MEMO
CONTENT:		MEMO RE: FOLLOW-UP TO SUBMISSION OF PROMOTINAL MATERIAL ON 26-AUG. CONTACT PERSON: FEATHER, K. VIA TELEPHONE MEMO FROM: MARTIN, I. ABSTRACT: REVIEW OF PROMOTIONAL MATERIALS NOT LIKELY UNTIL WEEK OF 09-SEP.
28-AUG-91		FDA CONTACT MEMO
CONTENT:		MEMO RE: COMMENT ON FPL SUBMISSION. CONTACT PERSON: BONGIOVANNI, K. VIA TELEPHONE MEMO FROM: MARTIN, I. AND SPIVEY, R. ABSTRACT: FPL FOR BLISTER PACKAGES TO BE SUBMITTED AFTER APPROVAL.
28-AUG-91		FDA CONTACT MEMO
CONTENT:		MEMO RE: DISCUSS ERROR IN FINAL PRINTED LABELING. CONTACT PERSON: TEMPLE, ROBERT VIA TELEPHONE MEMO FROM: MARTIN, I. ABSTRACT: DR. TEMPLE APPROVED MODIFICATION TO ADVERSE REACTION SECTION OF LABELING.
29-AUG-91		FDA CONTACT MEMO
CONTENT:		MEMO RE: FOLLOW-UP TO CONVERSTAION WITH DR. TEMPLE 28-AUG. CONTACT PERSON: CHEN, SHAW DR. VIA TELEPHONE MEMO FROM: MARTIN, I. ABSTRACT: DR. CHEN INFORMED OF LABELING ERROR.
29-AUG-91		FDA CONTACT MEMO
CONTENT:		MEMO RE: FOLLOW-UP TO CONVERSATION WITH DR. TEMPLE, 28-AUG. CONTACT PERSON: BONGIOVANNI, K. VIA TELEPHONE MEMO FROM: MARTIN, I. ABSTRACT: LABELING CHANGE DISCUSSED.

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29-AUG-91 51 LETTER RE: FINAL PRINTED LABELING  
CONTENT:

LETTER TO: LIPICKY, RAYMOND M.D.  
LETTER FROM: MARTIN, IRWIN  
RE: REFERENCE IS MADE TO PENDING NDA FOR ACCUPRIL  
(QUINAPRIL HCL) TABLETS, NDA 19-885.  
ADDITIONAL REFERENCE IS MADE TO OUR SUBMISSION OF  
DRAFT LABELING (FPL) ON 26-AUG-91 (NDA REF. 48).  
FURTHER REFERENCE IS MADE TO THE TELEPHONE  
CONVERSATION BETWEEN DR. ROBERT TEMPLE, OFFICE OF  
DRUG EVALUATION I, AND THE UNDERSIGNED ON 28-AUG-  
91 WHEREIN AN ERROR IN FPL WAS DISCUSSED. DR.  
TEMPLE WAS INFORMED THAT A PROGRAMMING ERROR WAS  
MADE DURING GENERATION OF THE LISTING OF ADVERSE  
REACTIONS. THE PARAGRAPH WHICH LISTS "CLINICAL  
ADVERSE EXPERIENCES PROBABLY OR POSSIBLY RELATED,  
OR PF UNCERTAIN RELATIONSHIP TO THERAPY OCCURRING  
IN 0.5% TO 1.0%...OF THE PATIENTS TREATED WITH  
ACCUPRIL..." ACTUALLY LISTED THESE ADVERSE  
EXPERIENCES REGARDLESS OF RELATIONSHIP TO THERAPY.  
CONTINUED - SEE CENTRAL FILE COPY.

30-AUG-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: NDA APPROVAL  
CONTACT PERSON: BONGIOVANNI, K. VIA IN PERSON  
MEMO FROM: MARTIN, I.  
ABSTRACT: DRAFT "FINAL" LABELING SUBMITTED. DR.  
TEMPLE OBJECTED TO THE LAUNCH ADVERTISING AND  
PROMOTION.

30-AUG-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: COMPLIANCE REPORT ON MOPS FACILITY AND  
IMPACT ON NDA APPROVAL.  
CONTACT PERSON: TEMPLE, R. VIA IN PERSON  
MEMO FROM: MARTIN, I.  
ABSTRACT: QUINAPRIL NOT APPROVED DUE TO  
REGULATORY CONCERNS WITH MOPS FACILITY.

30-AUG-91 52 LETTER RE: LABELING  
CONTENT:

LETTER TO: LIPICKY, RAYMOND  
LETTER FROM: MARTIN, IRWIN  
RE: REFERENCE IS MADE TO OUR PENDING NDA FOR  
ACCUPRIL (QUINAPRIL HYDROCHLORIDE) TABLETS, NDA  
19-885. ADDITIONAL REFERENCE IS MADE TO OUR  
SUBMISSION OF FINAL PRINTED LABELING ON 26-AUG-91  
(NDA REF #48), OUR SUBMISSION ON 29-AUG-91 (NDA  
RE #51) WHICH CONTAINED CORRECTIONS TO THE  
ADVERSE REACTIONS SECTION OF THE LABELING, AND TO  
TELEPHONE CONVERSATIONS WITH MS. KATHLEEN  
BONGIOVANNI OF YOUR DIVISION ON 27-AUG & 28-AUG-91  
IN WHICH MINOR CHANGES TO THE DESCRIPTION AND  
PRECAUTIONS, HYPERKALEMIA AND POTASSIUM-SPARING  
DIURETICS SECTIONS OF THE LABELING WERE REQUESTED.

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03-SEP-91  
CONTENT:

FDA CONTACT MEMO

MEMO RE: FOLLOW-UP TO FRIDAY NON-APPROVAL.  
CONTACT PERSON: BONGIOVANNI, K. VIA TELEPHONE  
MEMO FROM: MARTIN, I.  
ABSTRACT: MS. BONGIOVANNI UPDATED; FPL REQUESTED.

04-SEP-91  
CONTENT:

FDA CONTACT MEMO

MEMO RE: PROVIDE FPL  
CONTACT PERSON: BONGIOVANNI, K. VIA IN PERSON  
MEMO FROM: MARTIN, I.  
ABSTRACT: PROVIDE FPL.

04-SEP-91  
CONTENT:

53 LETTER RE: FINAL PRINTED LABELING

LETTER TO: LIPICKY, RAYMOND  
LETTER FROM: MARTIN, IRWIN  
RE: REFERENCE IS MADE TO OUR PENDING NDA FOR  
ACCUPRIL (QUINAPRIL HYDROCHLORIDE) TABLETS, NDA  
19-885.  
WE ARE NOW SUBMITTING FINAL PRINTED LABELING WHICH  
IS IDENTICAL TO THE TYPESET DRAFT LABELING  
SUBMITTED ON 30-AUG-91 (REF #52).  
WE WILL NOT MARKET ACCUPRIL UNTIL WE HAVE RECEIVED  
WRITTEN APPROVAL.  
QUESTIONS-----

05-SEP-91  
CONTENT:

FDA CONTACT MEMO

MEMO RE: STATUS OF WHAT I KNOW OF ACCUPRIL  
APPROVABILITY.  
CONTACT PERSON: BONGIOVANNI, K. VIA TELEPHONE  
MEMO FROM: MARTIN, I.  
ABSTRACT: MS. BONGIOVANNI UPDATED ON LATEST  
COMPLIANCE ISSUE. PENDING AMENDMENTS NEED TO BE  
WITHDRAWN PRIOR TO APPROVAL AND RESUBMITTED AS  
SUPPLEMENTS.

06-SEP-91  
CONTENT:

FDA CONTACT MEMO

MEMO RE: STATUS CHECK.  
CONTACT PERSON: BONGIOVANNI, K. VIA TELEPHONE  
MEMO FROM: MARTIN, I.  
ABSTRACT: NDA UPDATE PROVIDED.

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09-SEP-91 54 LETTER RE: NDA AMENDMENT - CMC FOR 40 MG TABLETS  
CONTENT:

LETTER TO: LIPICKY, RAYMOND  
LETTER FROM: BRENNAN, SEAN  
RE: ENCLOSED IS AN AMENDMENT TO OUR PENDING NDA  
19-885 FOR ACCURPIL (QUINAPRIL HYDROCHLORIDE)  
TABLETS FOR THE MANUFACTURING AND CONTROLS FOR A  
40 MG TABLET.  
ON 31-DEC-90, WE AMENDED THE PENDING NDA TO REMOVE  
THE 40 MG TABLET DUE TO LACK OF COMMERCIAL  
INTEREST AT THAT TIME.  
ON 01-MAY-91, DRS. I. MARTIN AND S. BRENNAN  
(PARKE-DAVIS) MET WITH DR. R. WOLTERS AND MS. D.  
CUNNINGHAM (CARDIO-RENAL DIVISION, CDER 1) TO  
DISCUSS A SUPPLEMENT FOR THE 40 MG TABLET. THERE  
WAS MUTAL AGREEMENT THAT THE SUPPLEMENT FOR THE  
40 MG TABLET SHOULD CONTAIN THE FOLLOWING:  
CONTINUED - SEE FILE COPY.

11-SEP-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: UPDATE ON PROMOTIONAL MATERIALS.  
CONTACT PERSON: FEATHER, K. VIA TELEPHONE  
MEMO FROM: MARTIN, I.  
ABSTRACT: MEETING DELAYED UNTIL NEW A&P MATERIAL  
SUBMITTED.

11-SEP-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: MUTUAL STATUS UPDATE.  
CONTACT PERSON: BONGIOVANNI, K. VIA IN PERSON  
MEMO FROM: MARTIN, I.  
ABSTRACT:  
- 40 MG TABLET RECEIVED.  
- TEMPLE'S OFFICE RECOMMENDS AGAINST GOING OVER  
THE DISTRICT'S HEAD.  
- MEETING WITH DRUG ADVERTISING DEPENDENT ON NEW  
A&P MATERIALS.

13-SEP-91 55 LETTER RE: FINAL PRINTED LABELING 10/20 MG BLISTER PACKAGE  
CONTENT:

LETTER TO: LIPICKY, RAYMOND  
LETTER FROM: MARTIN, IRWIN  
RE: REFERENCE IS MADE TO OUR PENDING NDA FOR  
ACCURPIL (QUINAPRIL HYDROCHLORIDE) TABLETS, NDA  
19-885, SUBMITTED 26-JAN-89. ADDITIONAL REFERENCE  
IS MADE TO SUBMISSION OF FINAL PRINTED LABELING ON  
26-AUG-91 (REF #48) AND TO TELEPHONE CONVERSATIONS  
WITH MS. K. BONGIOVANNI OF YOUR DIVISION ON 26-AUG  
27-AUG-91.  
AS AGREED IN THE ABOVE-REFERENCED TELEPHONE  
CONVERSATIONS, WE ARE NOW SUBMITTING FINAL PRINTED  
LABELS FOR THE 10 MG AND 20 MG UNIT DOSE BLISTER  
PACKAGES. WE WILL PROVIDE THE BLISTER PACKAGE  
LABEL FOR THE 5 MG TABLET PRIOR TO MARKETING THE  
5 MG UNIT-DOSE PACKAGE.



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CONTENT:

FDA CONTACT MEMO

MEMO RE: NDA UPDATE.  
CONTACT PERSON: BONGIOVANNI, K. VIA IN PERSON  
MEMO FROM: MARTIN, I.  
ABSTRACT: 40MG REVIEW TO BE COMPLETED SOON.

20-SEP-91  
CONTENT:

FDA CONTACT MEMO

MEMO RE: REQUEST PERMISSION TO USE OUR SLIDES  
(DRUG NAME DISGUISED) FOR DR. LIPICKY  
PRESENTATION OF 24-HOUR BLOOD PRESSURE  
DATA.  
CONTACT PERSON: BONGIOVANNI, K. VIA TELEPHONE  
MEMO FROM: SPIVEY, R.  
ABSTRACT: REQUEST PERMISSION TO USE OUR SLIDES  
(DRUG NAME DISGUISED) FOR DR. LIPICKY PRESENTATION  
OF 24-HOUR BLOOD PRESSURE DATA.

02-OCT-91  
CONTENT:

FDA CONTACT MEMO

MEMO RE: STATUS OF NDA; DELIVER ADVERTISING  
MATERIALS.  
CONTACT PERSON: BONGIOVANNI, K. VIA IN PERSON  
MEMO FROM: MARTIN, I.  
ABSTRACT: 40 MG TO BE APPROVED WITH NDA; A+P  
MATERIALS SUBMITTED.

02-OCT-91  
CONTENT:

LETTER RE: REVISED JOURNAL ADVERTISEMENT & SALES VISUAL AID

LETTER TO: WITT, ANN  
LETTER FROM: MARTIN, I.  
RE: REFERENCE IS MADE TO OUR PENDING NDA 19-885  
FOR ACCUPRIL (QUINAPRIL HYDROCHLORIDE) TABLETS.  
FURTHER REFERENCE IS MADE TO OUR PREVIOUS SUBMISS-  
ION OF OUR PROPOSED JOURNAL ADVERTISEMENT AND SALES  
VISUAL AID, SUBMITTED ON 26-AUG-91. WE ARE NOW  
SUBMITTING THE REVISED VERSION OF BOTH OF THESE  
DOCUMENTS FOR YOUR REVIEW. THESE MATERIALS HAVE  
ALSO BEEN FORWARDED TO THE DIVISION OF CARDIO-  
RENAL DRUG PRODUCTS UNDER SEPARATE COVER.  
PLEASE NOTE THAT THE REFERENCES SUBMITTED ON 26-  
AUG ALSO SUPPORT THE ENCLOSED MATERIALS.  
ADDITIONAL REFERENCES ARE ALSO ATTACHED.  
ALSO ENCLOSED IS A COPY OF OUR FINAL PRINTED  
LABELING WHICH WAS SUBMITTED ON 04-SEP-91.  
I WILL CONTACT YOUR DIVISION TO SCHEDULE A MEETING  
TO DISCUSS THE PROPOSED MATERIALS SUBMITTED  
HEREIN. QUESTIONS CONTACT ME----

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02-OCT-91 56 LETTER RE: INITIAL ADVERTISING CAMPAIGN, REVISED MATERIALS  
CONTENT:

LETTER TO: LIPICKY, RAYMOND M.D.  
LETTER FROM: MARTIN, I.  
RE: REFERENCE IS MADE TO OUR PENDING NDA 19-885  
FOR ACCUPRIL (QUINAPRIL HYDROCHLORIDE) TABLETS.  
REFERENCE IS ALSO MADE TO OUR PREVIOUS SUBMISSION  
OF PROPOSED ADVERTISING MATERIALS (REF #49, 26-AUG  
-91). WE HAVE ENCLOSED, FOR YOUR REVIEW, THE  
REVISED VERSION OF OUR PROPOSED 8-PAGE JOURNAL  
ADVERTISEMENT AND SALES FORCE VISUAL AID. THESE  
MATERIALS HAVE ALSO BEEN FORWARDED TO THE  
DIVISION OF MARKETING, ADVERTISING AND COMMUNICA-  
TIONS UNDER SEPARATE COVER.  
PLEASE NOTE THAT THE REFERENCES SUBMITTED ON  
26-AUG ALSO SUPPORT THE ENCLOSED MATERIALS.  
ADDITIONAL REFERENCES ARE ALSO ATTACHED.  
ALSO ENCLOSED IS A COPY OF OUR FINAL PRINTED  
LABELING, SUBMITTED ON 04-SEP-91 (REF #53).  
QUESTIONS CONTACT----

03-OCT-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: INFORM FDA OF STATUS OF CHF SUPPLEMENT.  
CONTACT PERSON: BONGIOVANNI, K. VIA IN PERSON  
MEMO FROM: SPIVEY, R.  
ABSTRACT: INFORM FDA OF STATUS OF CHF SUPPLEMENT.

04-OCT-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: STATUS OF QUINAPRIL A+P REVIEW.  
CONTACT PERSON: FEATHER, K. VIA TELEPHONE  
MEMO FROM: MARTIN, I.  
ABSTRACT: QUINAPRIL A+P MATERIALS UNDER REVIEW.

04-OCT-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: FOLLOW-UP TO 03-OCT CONVERSATION ON CHF  
APPLICATION.  
CONTACT PERSON: BONGIOVANNI, K. VIA TELEPHONE  
MEMO FROM: SPIVEY, R.  
DR. PHIL DERN WILL LIKELY BE ASSIGNED TO REVIEW  
QUINAPRIL CHF DATA.

07-OCT-91 FDA CONTACT MEMO  
CONTENT:

MEMO RE: FOLLOW-UP TO CONVERSATION WITH MR.  
FEATHER, 04-OCT-91.  
CONTACT PERSON: CHURNEY, I. VIA TELEPHONE  
MEMO FROM: MARTIN, I.  
ABSTRACT: ACCUPRIL A+P MATERIALS TO BE REVISED  
AGAIN PRIOR TO FDA MEETING.

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09-OCT-91  
CONTENT:

FDA CONTACT MEMO

MEMO RE: STATUS OF ADVERTISING REVIEW LETTER.  
CONTACT PERSON: CERNY, I. VIA TELEPHONE  
MEMO FROM: MARTIN, I.  
ABSTRACT: REVIEW LETTER RECEIVED.

09-OCT-91  
CONTENT:

LETTER RE: RESPONSE TO LAUNCH MATERIALS

LETTER TO: MARTIN, I.  
LETTER FROM: CERNY, IGOR  
RE: THIS LETTER IS IN RESPONSE TO YOUR ACCUPRIL  
LAUNCH MATERIALS SUBMITTED 26-AUG-91 AND REVISED  
MATERIALS SUBMITTED 02-OCT-91. BOTH THE JOURNAL  
AD (PD-103-JA-6112-A1) AND THE SALES VISUAL (PD-  
103-VA-6856-A1) CONTAIN NUMEROUS MISLEADING AREAS.  
THESE CONCERNS ARE OUTLINED BELOW THEMATICALLY:  
1) TISSUE ACE INHIBITION CLAIM : SEE FILE COPY.  
2) THE "REDUCE BLOOD PRESSURE SINGLE-HANDEDLY"  
CLAIM: SEE FILE COPY.  
3) MISCELLANEOUS: SEE FILE COPY.  
THIS LIST SHOULD NOT BE CONSIDERED EXHAUSTIVE AND  
WE SUGGEST THAT IN SUBSEQUENT SUBMISSIONS, THE  
LABELING OF THE PRODUCT IS STRICTLY ADHERED TO.  
AT THIS TIME A MEETING WOULD SEEM COUNTERPRO-  
DUCTIVE SINCE THE LAUNCH CAMPAIGN NEEDS MAJOR  
REVISION. WE AWAIT YOUR RESUBMISSION OF A REVISED  
PIECE.

18-OCT-91  
CONTENT:

LETTER RE: REVISED JOURNAL ADVERTISEMENT & SALES VISUAL AID

LETTER TO: WITT, ANNA  
LETTER FROM: MARTIN, IRWIN  
RE: REFERENCE IS MADE TO OUR PENDING NDA 19-885  
FOR ACCUPRIL (QUINAPRIL HYDROCHLORIDE) TABLETS.  
FURTHER REFERENCE IS MADE TO PREVIOUS SUBMISSIONS  
OF OUR PROPOSED JOURNAL ADVERTISEMENT AND SALES  
VISUAL AID, SUBMITTED ON 26-AUG AND 02-OCT, AND TO  
AN 09-OCT-91 LETTER FROM DR. IGOR CERNY OF YOUR  
DIVISION. WE ARE NOW SUBMITTING REVISED MATERIALS  
IN RESPONSE TO THE ABOVE-REFERENCED LETTER AND  
BELIEVE WE HAVE ADDRESSED THE STATED CONCERNS.  
HOWEVER, CONSISTENT WITH COMMON INDUSTRY PRACTICE,  
WE HAVE CONTINUED TO INCLUDE ONLY THE STARTING  
DOSE, 10 MG, IN ASSOCIATION WITH THE ACCUPRIL NAME  
ON THE COVER PAGE. PURSUANT TO 21 CFR 202.1 (D) (2),  
WE BELIEVE ONE TABLET STRENGTH NEEDS TO BE  
MENTIONED IN THE ADVERTISEMENT.  
CONTINUED - SEE FILE COPY.

REGULATORY LIAISON AND COMPLIANCE  
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DOC DATE SER/SUPPL NO TITLE

18-OCT-91

FDA CONTACT MEMO

CONTENT:

MEMO RE: DELIVER REVISED A+P MATERIAL.  
CONTACT PERSON: CERNY, I. VIA IN PERSON  
MEMO FROM: MARTIN, I.  
ABSTRACT: REVISED A+P LAUNCH MATERIALS PROVIDED.

18-OCT-91

FDA CONTACT MEMO

CONTENT:

MEMO RE: DELIVER DESK COPIES AND UPDATE STATUS.  
CONTACT PERSON: BONGIOVANNI, K. VIA IN PERSON  
MEMO FROM: MARTIN, I.  
ABSTRACT: APPROVAL LETTER TO BE UPDATED WITH NEW SUBMISSIONS.

18-OCT-91

FDA CONTACT MEMO

CONTENT:

MEMO RE: REQUEST FOR 10/24 ADVISORY COMMITTEE MEETING.  
CONTACT PERSON: CHEN, S. VIA IN PERSON  
MEMO FROM: MARTIN, I.  
ABSTRACT: KEY TO 'BESTAPRIL' SLIDES REQUESTED.

18-OCT-91  
CONTENT:

57 LETTER RE: FINAL PRINTED LABELING 40 MG BLISTER PACKAGE

LETTER TO: LIPICKY, RAYMOND MD  
LETTER FROM: MARTIN, IRWIN  
RE: REFERENCE IS MADE TO OUR PENDING NDA FOR ACCUPRIL (QUINAPRIL/HYDROCHLORIDE) TABLETS, NDA 19-885, SUBMITTED 26-JAN-89. FURTHER REFERENCE IS MADE TO OUR AMENDMENT (REF #54, 09-SEP-91) TO INCLUDE MANUFACTURING AND CONTROLS FOR A 40 MG TABLET.  
WE ARE NOW SUBMITTING FINAL PRINTED LABELS FOR THE 40 MG UNIT DOSE BLISTER PACKAGES.  
QUESTION CALL-----

18-OCT-91  
CONTENT:

58 LETTER RE: REVISED JOURNAL ADVERTISEMENT & SALES VISUAL AID

LETTER TO: LIPICKY, RAYMOND  
LETTER FROM: MARTIN, IRWIN  
RE: REFERENCE IS MADE TO OUR PENDING NDA 19-885 FOR ACCUPRIL (QUINAPRIL HYDROCHLORIDE) TABLETS. FURTHER REFERENCE IS MADE TO PREVIOUS SUBMISSIONS OF OUR PROPOSED JOURNAL ADVERTISEMENT AND SALES VISUAL AID, SUBMITTED ON 26-AUG AND 02-OCT, AND TO AN 09-OCT-91 LETTER FROM DR. IGOR CERNY OF THE DIVISION OF DRUG MARKETING, ADVERTISING AND COMMUNICATIONS. WE ARE NOW SUBMITTING REVISED MATERIALS IN RESPONSE TO THE ABOVE-REFERENCED LETTER AND BELIEVE WE HAVE ADDRESSED THE STATED CONCERNS. HOWEVER, CONSISTENT WITH COMMON INDUSTRY PRACTICE, WE HAVE CONTINUED TO INCLUDE ONLY THE STARTING DOSE, 10 MG, IN ASSOCIATION WITH THE ACCUPRIL NAME ON THE COVER PAGE. PURSUANT TO

21 CFR 202.1 (D) (2), WE BELIEVE ONE TABLET STRENGTH  
NEEDS TO BE MENTIONED IN THE ADVERTISEMENT.  
CONTINUED - SEE FILE COPY.

REGULATORY LIAISON AND COMPLIANCE  
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DOC DATE SER/SUPPL NO TITLE

21-OCT-91  
CONTENT:

FDA CONTACT MEMO

MEMO RE: PROVIDE INFORMATION ON CODING SCHEMES  
USED FOR "BESTAPRIL" SLIDES FOR CARDIO-  
RENAL ADVISORY COMMITTEE MEETING.  
CONTACT PERSON: CHEN, S. VIA TELEPHONE  
MEMO FROM: SPIVEY, R.  
ABSTRACT: PROVIDE INFORMATION ON CODING SCHEMES  
USED FOR "BESTAPRIL" SLIDES FOR CARDIO RENAL  
ADVISORY COMMITTEE MEETING; 03-OCT.

23-OCT-91  
CONTENT:

FDA CONTACT MEMO

MEMO RE: STATUS OF A+P REVIEW (10/18 SUBMISSION).  
CONTACT PERSON: CERNY, I. VIA TELEPHONE  
MEMO FROM: MARTIN, I.  
ABSTRACT: RECENT SUBMISSION OF A+P MATERIALS STILL  
NEED REVISION.

24-OCT-91  
CONTENT:

LETTER RE: LAUNCH PROMOTIONAL MATERIALS

LETTER TO: SMITH, JOSEPH  
LETTER FROM: CERNY, IGOR  
RE: THIS IS IN REFERENCE TO LAUNCH PROMOTIONAL  
MATERIALS FOR ACCUPRIL SUBMITTED TO US ON 18-OCT-  
91 IDENTIFIED AS PD-103-JA-6112-A1 AND PD-103-VA-  
6856-A1.  
YOUR 18-OCT-91 SUBMISSION REPRESENTS THE SECOND  
REVISION OF THESE LAUNCH MATERIALS. HOWEVER, YOUR  
THIRD BATCH OF LAUNCH MATERIALS CONTAINS NEARLY  
IDENTICAL FALSE AND MISLEADING ITEMS WHICH WERE  
OBJECTED TO INITIALLY. OUR 09-OCT-91 LETTER TO  
I. MARTIN, CLEARLY OUTLINES THE AREAS OF THE  
PROMOTIONAL PIECES WHICH WE FIND OBJECTIONABLE.  
FOR YOUR CONVINIENCE, THESE OBJECTIONABLE AREAS  
ARE REITERATED BELOW.  
CONTINUED - SEE FILE COPY.

29-OCT-91  
CONTENT:

FDA CONTACT MEMO

MEMO RE: FOLLOW-UP TO 23-OCT CONTACT RE: MEETING  
REQUEST.  
CONTACT PERSON: CERNY, I. VIA TELEPHONE  
MEMO FROM: MARTIN, I.  
ABSTRACT: NEW LETTER SENT ON A+P MATERIALS.

29-OCT-91  
CONTENT:

FDA CONTACT MEMO

MEMO RE: FOLLOW-UP ON 24-OCT LETTER TO J. SMITH  
RE: LAUNCH MATERIALS.  
CONTACT PERSON: FEATHER, K. VIA TELEPHONE  
MEMO FROM: MARTIN, I.  
ABSTRACT: FRUSTRATION OVER 24-OCT LETTER VENTED.

CI NUMBER= 906 APPL NUMBER= 19-885

DOC DATE SER/SUPPL NO TITLE

29-OCT-91  
CONTENT:

FDA CONTACT MEMO

MEMO RE: GET MEETING DATE PREFERENCES.  
CONTACT PERSON: CERNY, I. VIA TELEPHONE  
MEMO FROM: MARTIN, I.  
ABSTRACT: BACKGROUND PACKAGE TO BE PROPOSED FOR  
ADVISORY MEETING.

30-OCT-91  
CONTENT:

FDA CONTACT MEMO

MEMO RE: MEETING DATE FOR ADVERTISING REVIEW  
MEETING.  
CONTACT PERSON: CERNY, I. VIA TELEPHONE  
MEMO FROM: MARTIN, I.  
ABSTRACT: MEETING DATE STILL NEEDED.

04-NOV-91  
CONTENT:

LETTER RE: PROPOSED JOURNAL ADVERTISEMENT & SALES VISUAL AID

LETTER TO: WITT, ANN  
LETTER FROM: MARTIN, I.  
RE: REFERENCE IS MADE TO OUR PENDING NDA 19-885  
FOR ACCUPRIL (QUINAPRIL HYDROCHLORIDE) TABLETS.  
FURTHER REFERENCE IS MADE TO PREVIOUS SUBMISSIONS  
OF OUR PROPOSED JOURNAL ADVERTISEMENT AND SALES  
VISUAL AID, SUBMITTED ON 26-AUG, 02-OCT, AND  
18-OCT-91. ADDITIONAL REFERENCE IS MADE TO 09-OCT  
AND 24-OCT LETTER FROM DR. IGOR CERNY OF YOUR  
DIVISION.  
IN THE 24-OCT LETTER DR. CERNY STATES THAT OUR  
REVISED MATERIALS "CONTAIN NEARLY IDENTICAL FALSE  
AND MISLEADING ITEMS AS WERE OBJECTED TO  
INITIALLY." WE BELIEVE WE ADDRESSED THESE  
COMMENTS. REVIEWED BELOW ARE THE INITIAL  
OBJECTIONS AND OUR COMMENTS.  
CONTINUED - SEE FILE COPY.

04-NOV-91  
CONTENT:

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LETTER RE: PROPOSED JOURNAL ADVERTISEMENT & SALES VISUAL AID

LETTER TO: LIPICKY, RAYMOND M.D.  
LETTER FROM: MARTIN, IRWIN  
RE: REFERENCE IS MADE TO OUR PENDING NDA 19-885  
FOR ACCUPRIL (QUINAPRIL HYDROCHLORIDE) TABLETS.  
FURTHER REFERENCE IS MADE TO PREVIOUS SUBMISSIONS  
OF OUR PROPOSED JOURNAL ADVERTISEMENT AND SALES  
VISUAL AID, SUBMITTED ON 26-AUG, 02-OCT, AND  
18-OCT-91. ADDITIONAL REFERENCE IS MADE TO 09-OCT  
AND 24-OCT LETTERS FROM DR. IGOR CERNY, DIVISION  
OF MARKETING, ADVERTISING AND COMMUNICATIONS.  
IN THE 24-OCT LETTER DR. CERNY STATES THAT OUR  
REVISED MATERIALS "CONTAIN NEARLY IDENTICAL FALSE  
AND MISLEADING ITEMS AS WERE OBJECTED TO  
INITIALLY." WE BELIEVE WE ADDRESSED THESE  
COMMENTS. REVIEWED BELOW ARE THE INITIAL  
OBJECTIONS AND OUR COMMENTS.  
CONTINUED - SEE FILE COPY.

REGULATORY LIAISON AND COMPLIANCE  
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CI NUMBER= 906 APPL NUMBER= 19-885

DOC DATE SER/SUPPL NO TITLE

05-NOV-91  
CONTENT:

FDA CONTACT MEMO

MEMO RE: PROVIDE DESK COPIES; UPDATE NDA STATUS.  
CONTACT PERSON: BONGIOVANNI, K. VIA IN PERSON  
MEMO FROM: MARTIN, I.  
ABSTRACT: NDA WILL BE APPROVED FOR 36 MONTH  
EXPIRATION DATING. STATUS OF APPROVAL AND FUTURE  
LABELING CHANGES DISCUSSED. ACCURETIC MAY HAVE  
1991 APPROVABLE STATUS.

06-NOV-91  
CONTENT:

FDA CONTACT MEMO

MEMO RE: STATUS OF MOPS INSPECTION.  
CONTACT PERSON: WOLTERS, R. VIA TELEPHONE  
MEMO FROM: MARTIN, I.  
ABSTRACT: DR. WOLTERS TO BE CALLED UPON MOPS  
APPROVAL.

13-NOV-91  
CONTENT:

FDA CONTACT MEMO

MEMO RE: STATUS OF INSPECTION.  
CONTACT PERSON: BONGIOVANNI, K. VIA IN PERSON  
MEMO FROM: MARTIN, I.  
ABSTRACT: UPDATED STATUS OF MOPS AND HOLLAND  
INSPECTIONS.

13-NOV-91  
CONTENT:

FDA CONTACT MEMO

MEMO RE: CLARIFY 19-NOV MEETING ATTENDEES.  
CONTACT PERSON: CERNY, I. VIA IN PERSON  
MEMO FROM: MARTIN, I.  
ABSTRACT: ATTENDEES CLARIFIED.

15-NOV-91  
CONTENT:

FDA CONTACT MEMO

MEMO RE: STATUS OF NDA APPROVAL LETTER.  
CONTACT PERSON: CARTER, L. VIA TELEPHONE  
MEMO FROM: MARTIN, I.  
ABSTRACT: APPROVAL EXPECTED 18-NOV.

19-NOV-91  
CONTENT:

LETTER RE: APPLICATION APPROVED EFFECTIVE

LETTER TO: MARTIN, IRWIN  
LETTER FROM: TEMPLE, ROBERT  
RE: PLEASE REFER TO YOUR 26-JAN-91 NDA SUBMITTED  
FOR ACCUPRIL (QUINAPRIL HYDROCHLORIDE) 5, 10, 20,  
AND 40 MG TABLETS.  
WE ALSO ACKNOWLEDGE RECEIPT OF YOUR AMENDMENTS AND  
CORRESPONDENCE DATED 23 & 24-MAY, 20, 21, 22,  
26 (TWO), 29, & 30-AUG, 04, 09, & 13-SEP, 02 AND  
18 (TWO)-OCT AND 04-NOV-91.  
WE HAVE COMPLETED THE REVIEW OF THIS APPLICATION  
AND HAVE CONCLUDED THAT ADEQUATE INFORMATION HAS  
BEEN PRESENTED TO DEMONSTRATE THAT THE DRUG IS



SAFE AND EFFECTIVE FOR USE AS RECOMMENDED IN THE  
FINAL PRINTED LABELING SUBMITTED 09-SEP-91  
(PACKAGE INSERT) AND 26-AUG, 09 & 16-SEP, AND  
18-OCT-91 (CARTON AND CONTAINER LABELS).  
ACCORDINGLY, THE APPLICATION IS APPROVED EFFECTIVE  
ON THE DATE OF THIS LETTER.  
CONTINUED - SEE FILE COPY.